Obesity

Definition
Increased body weight due to excessive amounts of fat; partly due to genetic disposition.

Object Perception

Definition
►Form Perception

Object-based Attention

Definition
Object-based attention refers to mechanisms by which an entire object is selected for further processing. Object-based attention will spread to all features of the selected object. For instance, if subjects perform a task on the shape of an object, the processing of the color of the object will also be enhanced. In addition, if subjects are attending to only a portion of the object, attention will spread over the entire spatial extent of the object (see Visual attention).

►Visual Attention

OBPs

►Odorant Receptor

Observability

Definition
Observability represents the ability to detect (observe) physical system behavior by means of the sensors connected to it. In terms of system states, it is the ability to infer state values using sensor outputs.

►Control

Observational Learning

Definition
Learning that occurs as a function of observing, retaining and replicating behavior observed in others. Observation[al] learning is a looser concept than imitation learning. Social learning is a type of observation[al] learning. Motivation, attention and/or simple paring of novel stimuli may contribute to this process. Thus even invertebrates such as octopus can perform observation[al] learning (Florito and Scotto, 1992).

►Imitation Learning

Obsessive-compulsive Disorder [OCD]

Definition
A neurotical disease (in DSM-IV: anxiety disorder) in which the mind is flooded with persistent and uncontrollable thoughts or the individual is compelled to repeat certain acts again and again, causing significant distress and interference with everyday functioning.

►Personality Disorder

Obstructive Sleep Apnea

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Synonyms

Sleep apnea; Obstructive sleep apnea hypopnea syndrome; Obstructive sleep-disordered breathing

Definition

►Apnea: a cessation in ventilatory airflow lasting for 10 s or longer.

►Sleep apnea: A diverse group of disorders with a common feature of repeated sleep-dependent cessations in airflow.

►Obstructive sleep apnea: A syndrome in which repeated cessations in airflow occur as a direct consequence of sleep-dependent collapse of the upper airway. The syndrome is characterized by sleepiness, fatigue and snoring.

Characteristics

Overview

Obstructive sleep apnea is a rapidly evolving syndrome. For decades, snoring was believed to be more of an inconvenience for the bed partner than a sign of significant disease. Recent studies, however, have clearly established that snoring in association with unrefreshed sleep is a warning sign of obstructive sleep apnea, and obstructive sleep apnea is now widely recognized as an independent risk factor for significant cardiovascular and neurological morbidities. Therefore, obstructive sleep apnea is a disorder for which high clinical suspicion, early diagnosis, and effective intervention are of utmost importance.

Pathogenesis

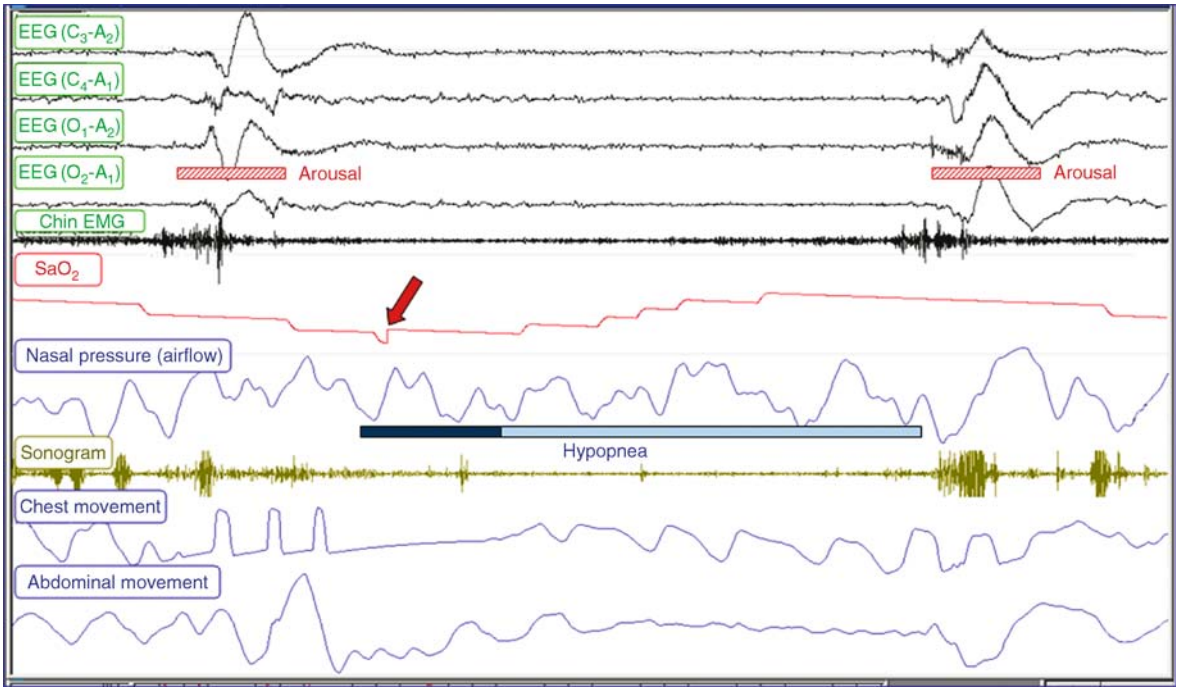
A unique feature of disorders of sleep apnea is that the brief cessations in ventilation occur exclusively in sleep. In wakefulness, neural mechanisms ensure continued respiration. In sleep, both ►non-rapid-eye-movement (NREM) and/or ►rapid-eye-movement (REM) sleep, ventilatory drive may fall sufficiently to allow apneas to develop. The obstructive nature of events occurs in part because ►NREM and ►REM sleep are associated with reductions in muscle activity, with a greater decline in ►pharyngeal muscle activity than reduction in pump muscle activity [1]. This occurs as a normal physiological response to sleep in all individuals. However, individuals with obstructive sleep apnea rely upon specific muscles surrounding the pharynx to stent open the airway for ventilation. Because the ►oropharynx is a highly collapsible tube, and one that may be collapsed from any direction, a number of pharyngeal muscles must act in concert to stent open the pharynx. These pharyngeal muscles include the tongue (►genioglossus), ►soft palate muscles, and muscles that stiffen the posterior wall or extend the lateral walls of the pharynx. In sleep, reductions in upper airway dilator muscle tone result in collapse of the upper airway [1]. Collapse of the upper airway is most likely to occur during inspiration, when negative pressures are generated in the lumen of the oropharynx [1]. Occlusion of the upper airway results in cessation of airflow, or apnea, that in turn results in ►hypercapnia, hypoxia and stimulation of upper airway afferents, resulting in arousal and resumption of the necessary upper airway muscle activity to reopen the upper airway. This process can be repeated up to 100 times/h of NREM and REM sleep. In many individuals, the slee p-dependent events involve a reduction in flow, rather than complete cessation of flow. A sleep-related reduction in flow, associated with a drop in oxygen saturation and an arousal, is termed a ►hypopnea. These events disrupt sleep and oxygenation and are considered as clinically significant as ►apneas. One of these events is illustrated in Fig. 1, showing a reduction in airflow just at sleep onset, result in a drop in oxygen saturation and arousal.

The intermittent hypoxia and frequent arousals from both apneas and hypopneas can increase sympathetic activity and induce inflammatory and smooth muscle changes in vessels, exacerbating hypertension and ►atherosclerosis. In addition, recent studies suggest the intermittent hypoxia can result in irreversible cognitive impairments and neural injury.

Epidemiology

Symptomatic obstructive sleep apnea is present in 4–7% of adult males and 2–3% of adult females in North America, Europe and in select regions of Asia [2]. Despite the 2:1 male:female predominance in adults, there are no apparent gender differences in ►OSA prevalence in pre-pubertal children. Prevalence increases with age and is estimated to approach 40% in elderly individuals. While prevalence does not vary with race, the severity of OSA is greater in age-matched African American individuals than in Caucasians, and it appears that OSA develops at an earlier age in African Americans than in Caucasians. Familial aggregation has been established for OSA. Approximately 40% of the variance in the apnea hypopnea frequency may be explained by familial factors, and a positive family history increases the relative risk by 2- to 4-fold [2]. How much of this variance is simply ►obesity remains to be determined [2].

►Craniofacial anomalies that compromise upper airway space and stability provide additional risk



Obstructive Sleep Apnea. Figure 1 Polysomnography for the diagnosis of obstructive sleep apnea. The electroencephalographic activity across the frontal, parietal and occipital cortices, is present in the top four channels. Channel 5 shows the chin elctromyogram. The arterial saturation (SaO_2) is presented in channel 6, and airflow measured with a nasal pressure transducer, the snore signal and chest and abdominal movements are shown below. An arousal from one hypopnea, underlined by the first red bar, is rapidly followed by sleep onset an another hypopnea. The hypopnea terminates with the second arousal, underlined by a red line. Notice the SaO_2 appears to fall just after the arousal. This is attributed to a delay in circulation time required for detection of the peripheral signal. Notice the snoring is quiet across the hypopnea when little airflow is exchanged. Polysomnography typically records four additional channels for leg movements, electrocardiogram and eye movements. These signals were removed to highlight the respiratory events.

factors for OSA. For example, ►micrognathia in ►Treacher-Collins syndrome and ►Pierre-Robin syndrome and ►maxillary insufficiency in ►Down and ►Apert syndromes predispose to collapsible upper airways. ►Hypothyroidism and ►acromegaly increase tongue soft tissue that impinges upon the oropharynx. The most common risk factor for OSA, however, is obesity, defined in adults as a body mass index >30 kg/m^2. In children, the major risk factor for OSA has been enlarged ►adenoid and ►tonsillar tissue. With the increasing prevalence of childhood obesity, obesity is becoming the major risk factor for OSA in children as well as in adults. A minority of patients diagnosed with OSA is non-obese. In these cases, chronic nasal obstruction from allergies, ►polyps or ►septal deviation, or craniofacial variances, e.g., ►retrognathia or ►macroglossia, may contribute to the increased collapsibility of the upper airway and OSA. In summary, the most important risk factor for OSA is obesity. Nonetheless, it is important to recognize that OSA occurs in diverse groups of patients, and in light of the significant neurobehavioral and cardiovascular morbidities, it is important to explore the possibility of OSA in all individuals presenting with snoring and unrefreshed sleep or poor sleep quality.

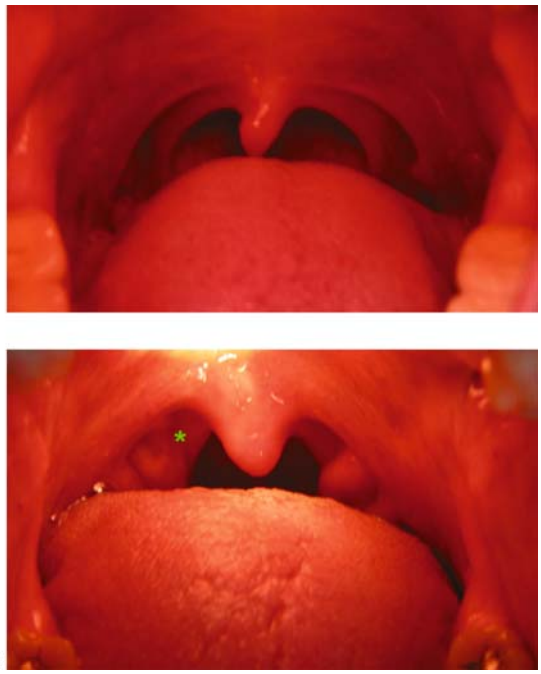
Presentation and Diagnosis

The presence of snoring and excessive sleepiness or fatigue despite adequate time allowed for sleep (7–9 h) in adults should prompt evaluation for OSA. It is important to recognize that in females and in children the presentation may be less straightforward. In both women and children, the snoring may be subtle, and rather than sleepiness, adult females may complain of fatigue or insomnia. Children are far more likely to exhibit increased motor activity, poor performance in school, and/or impulsive behavior than to have daytime sleepiness. Snoring alone does not make a good screening tool. In the United States, habitual snoring is present in 40% of adult males, 20% of adult females and 10% of children. Thus, it is essential to identify associated neurobehavioral complaints in snorers, e.g., unrefreshed sleep, fatigue, insomnia, restless sleep or irritability before proceeding with diagnostic testing.

The physical exam in many individuals in which a clinical suspicion for OSA is raised will suggest upper airway compromise. A neck circumference (>17 in. in adult males or >15 in. in adult females, a low lying soft palate, a small space behind the soft palate, large tonsils, a small mandible, and thickened lateral walls of the oropharynx all suggest increased upper airway collapsibility. Figure 2 shows a typical oropharynx in a person with mild OSA. There is no obvious obstruction.

The tonsils and tonsillar pillars are somewhat medial and may result in lateral wall collapse in sleep, but it is entirely possible that the point of initial collapse is lower in the airway or caused by retrograde placement of the tongue in sleep. Because airway examination occurs with the patient awake, a clear obstruction is unlikely to be identified.

The gold standard diagnostic tool for OSA is ►polysomnography. Polysomnography refers to the recording of multiple physiological signals during sleep [3]. Electroencephalographic and electromyographic signals are used to score specific sleep stages, as described elsewhere in this text. Airflow is measured indirectly with use of a thermistor, or with a nasal pressure transducer, and chest and abdominal movements are measured using piezosensors or strain gauges. Arterial oxygenation is recorded with ►pulse oximetry. An example of 30 s polysomnographic recording is presented in Fig. 1.



Obstructive Sleep Apnea. Figure 2 Upper airway physical findings. (a) top panel shows a normal wide oropharynx. (b) In this individual with mild OSA, the tonsils are only mildly enlarged and the soft palate (uvula) is readily visible with some lateral wall narrowing at the tonsillar pillars (*).

Complimentary channels include channels to detect leg movements or snoring and the electrocardiogram. The diagnosis of OSA in adults requires >5 apneas or hypopneas/h, on average, across sleep with symptoms, as above [3]. In children, neurobehavioral symptoms and an ►apnea index >1 is sufficient for the diagnosis. Presently, the majority of polysomnographies are performed in clinical sleep laboratories; however, because obesity is on the rise and the clinical suspicion for OSA is heightened, it is anticipated that there will be a shift in the near future towards the implementation of simpler, more cost-effective screening tools for OSA.

Treatment

The primary goal of therapy for OSA is to prevent collapse of the upper airway. The mainstay therapy for OSA is a remarkably effective mechanical therapy; ►positive airway pressure (PAP) titrated to an optimal pressure in each individual can fully prevent collapse of the upper airway in all stages of sleep in almost all patients with OSA [4]. Each individual with OSA will require a unique pressure to stent open her upper airway across all of NREM and REM sleep. The pressure needed will vary with sleep stage (NREM sleep vs. REM sleep) and with position and with nasal obstruction and sleeping position [4]. All of these factors must be taken into consideration when identifying the optimal pressure to alleviate OSA. Thus, a properly performed titration must confirm that apneas and hypopneas are alleviated in all sleep stages, all sleeping positions and that sleep is less fragmented. The latter ensures that subtle events have also been prevented. Prescribed pressures typically vary between 5 and 15 cm H_2O. Although remarkably effective for OSA, PAP therapy is cumbersome, requiring a tightly fitted mask over the nose and/or mouth. Figure 3 shows one of the newer PAP interfaces that allows an individual improved visibility for reading prior to sleep onset.

Despite advancements in mask comfort and PAP delivery, less than half of the individuals prescribed PAP regularly use this therapy. Nonetheless, every effort should be made in individuals to encourage use of PAP regularly, as this is the only therapy for OSA shown to lessen cardiovascular and neurobehavioral morbidity. For patients with claustrophobia and other mask difficulties, behavioral therapy to adjust to mask use has been shown highly effective. Recent developments in PAP therapy include machines that can self-adjust the level of PAP based on airflow patterns, and these, too, may increase usage in select groups of patients [4].

Alternative therapies for OSA should be considered in individuals with mild sleep apnea and in individuals unable to acclimate to PAP use. These alternative

Obstructive Sleep Apnea. Figure 3 Continuous positive airway pressure interface. This system is designed to deliver positive airway pressure to the nares and allow improved visibility. Flexible tubing connects the nasal mask to a small air pump to deliver positive pressure. Newer machines have the capability of detecting snoring, apneas and hypopneas, hours of usage and mask leaks.

therapies include surgical procedures to shorten the soft palate and reduce collapsibility of the pharynx (►uvulopalatoplasty), or to reduce the tongue volume (►genioglossectomy) or to advance the genioglossus forward (genioglossus advancement hyoid myotomy). These therapies in select groups of patients are expected to improve OSA in 50% of patients [5]. In patients with persistent symptomatic OSA, a second phase of surgery may be necessary to increase pharyngeal space (maxillary advancement or maxillary and ►mandibular osteotomy). Laser-assisted uvulopalatoplasty and temperature-controlled radio frequency are most effective for benign snoring. Some patients who do not tolerate PAP or in whom OSA is mild may benefit from oral appliances that advance the mandible. As with surgical therapies, the oral appliances are most likely to work in individuals with mild disease.

Weight loss should be recommended in all obese individuals with OSA. Dietary counseling should be the first step taken, and all patients should understand that reduced caloric intake is the critical factor for successful weight loss. Behavioral modification programs enhance sucess of weight loss. Exercise may help maintain weight, but in most non-athletic individuals, healthy caloric restriction should be the primary strategy for weight loss. ►Bariatric surgery should be reserved for individuals with morbid obesity who have failed dietary weight loss programs. The majority of individuals who have substantial weight loss after bariatric surgery will experience marked reductions in OSA, if not lasting reversal of the disease [6]. Treatment of OSA in persons with hypothyroidism or acromegaly should begin with PAP therapy, but across the treatment of the underlying endocrine disorder the PAP settings may need adjusting, as the soft tissues remodel. Several medical therapies for OSA may be considered as second line therapies for mild OSA. There may be subsets of individuals who respond to supplemental oxygen, positional therapy and rarely to pharmacotherapies such as selective serotonin reuptake drugs in individuals with mild ►REM sleep-predominant apnea [7]. Because these adjunctive therapies are rarely fully effective, treatment success should be determined with repeated polysomnography.

Stimulant therapy to reduce residual sleepiness in treated OSA has been recently examined [8]. The effect size for objective sleepiness is small, and it should be understood that individuals with residual sleepiness remain at high risk for motor vehicle accidents.

Associated Morbidities

One of the most important advances in OSA has been the substantiation of OSA as an independent risk factor for cardiovascular, endocrine and neurological morbidities. OSA is now widely accepted as an independent risk factor for several cardiovascular diseases, including hypertension, congestive heart failure, and stroke [9]. Importantly, the relative risk for hypertension increases even at levels of mild OSA (5–15 events/h), and use of PAP therapy can reduce this risk. The rates of significant cardiovascular events across 10 years in a large prospective European trial were found to be fourfold larger in untreated vs. treated untreated OSA [10]. The risk of cardiovascular death is also reduced with PAP therapy in persons with severe OSA [10]. Children with OSA show left ventricular dysfunction and increased levels of circulating inflammatory markers associated with atherosclerosis [9]. The mechanisms are poorly understood, but contributing factors include increased sympathetic activity, endothelial inflammation and ►oxidative stress [9]. In light of the seriousness of morbidities and the disease interactions associated with OSA, even in children, every effort to treat OSA effectively should be made. There have been several recent reports suggesting that OSA is an independent risk factor for insulin resistance. This risk persists after controlling for obesity, and several

studies have demonstrated improvement in glucose control and insulin sensitivity with successful use of PAP therapy. Whether long-term PAP therapy reduces the occurrence of complications of diabetes remains to be studied. Several recent reports suggest that OSA may impair liver function and might contribute to non-alcoholic fatty liver disease, a major risk for liver failure in developed countries. OSA is an independent risk factor for motor vehicle crashes, raising the relative risk by 2.5-fold, and a direct link between OSA and motor vehicle accidents is supported by the reduction in car crash risk with successful treatment of sleep apnea.

Future Directions

►Obstructive sleep apnea is now widely accepted as a serious disorder, associated with significant morbidity. The importance of recognition and treatment of obesity in children and young adults is critical for reducing the prevalence of this disorder. For the millions of individuals with undiagnosed OSA, there is a readily appreciable need to improve screening methodologies to dramatically increase availability. PAP is a remarkably effective therapy and efforts to improve its acceptance must continue, while we await the development of effective pharmacotherapies.

References

1. Remmers JE, deGroot WJ, Sauerland EK, Anch AM (1978) Pathogenesis of upper airway occlusion during sleep. J Appl Physiol 44(6):931–938
2. Palmer LJ, Redline S (2003) Genomic approaches to understanding obstructive sleep apnea. Respir Physiol Neurobiol 135(2–3):187–205
3. Redline S, Budhiraja R, Kapur V, Marcus CL, Mateika JH, Mehra R, Parthasarthy S, Somers VK, Strohl KP, Sulit LG, Gozal D, Wise MS, Quan SF (2007) The scoring of respiratory events in sleep: reliability and validity. J Clin Sleep Med 3(2):169–200
4. Basner RC (2007) Continuous positive airway pressure for obstructive sleep apnea. N Engl J Med 356(17):1751–1758
5. Elshaug AG, Moss JR, Southcott AM, Hiller JE (2007) Redefining success in airway surgery for obstructive sleep apnea: a meta analysis and synthesis of the evidence. Sleep 30(4):461–467
6. Fritscher LG, Canani S, Mottin CC, Fritscher CC, Berleze D, Chapman K, Chatkin JM (2007) Bariatric surgery in the treatment of obstructive sleep apnea in morbidly obese patients. Respiration 74(6):647–652
7. Veasey SC, Guilleminault C, Strohl KP, Sanders MH, Ballard RD, Magalang UJ (2006) Medical therapy for obstructive sleep apnea: a review by the Medical Therapy for Obstructive Sleep Apnea Task Force of the Standards of Practice Committee of the American Academy of Sleep Medicine. Sleep 29(8):1036–1034
8. Santamaria J, Iranzo A, Ma Montserrat J, de Pablo J (2007) Persistent sleepiness in CPAP treated obstructive sleep apnea patients: evaluation and treatment. Sleep Med Rev 11(3):195–207
9. McNicholas WT, Bonsigore MR (2007) Sleep apnoea as an independent risk factor for cardiovascular disease: current evidence, basic mechanisms and research priorities. Eur Respir J 29(1):156–178
10. Marin JM, Carrizo SJ, Vicente E, Agusti AG (2005) Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet 365(9464):1046–1053

Obstructive Sleep-disordered Breathing

►Obstructive Sleep Apnea

Occipital Cortex

Definition

The posterior part of the cerebral cortex.

Occipital Lobe

Synonyms

Lobus occipitalis

Definition

Extends from the occipital pole to the parietooccipital sulcus.

►Telencephalon

Occlusal Table

Definition

The space between the upper and lower teeth.

►Tactile Sensation in Oral Region

Occlusion

Definition
Artificial increase in low-frequency level produced by blocking the ear canal.

►Hearing Aids

Occlusion in Audition

Definition
Artificial increase in low-frequency level produced by blocking the ear canal.

►Hearing Aids

Octaval Nuclei

Definition
Primary hindbrain recipient targets for inner ear afferents. This complex of nuclei may be homologous (in whole or in part) with the mammalian cochlear nuclei complex.

►Evolution of Mechanosensory and Electrosensory Lateral Line Systems

Octave

Definition
The ratio between two sound frequencies of two.

►Acoustics

Octavolateralis System

Definition
A set of sensory organs, both mechanosensitive and electrosensitive, in aquatic vertebrates that are innervated by the eighth cranial nerve and by the lateral line nerves. More specifically: the sense of hearing, the sense of equilibrium, the sense of rotation, the mechanosensitive lateral line system, and the electric sense.

►Electroreceptor Organs
►Evolution of the Mechanosensory and Electrosensory Lateral Line Systems

Octopus Cells

Definition
Typical neuron of the posteroventral cochlear nucleus (PVCN) that receive small auditory nerve terminals on their dendrites and project to the ventral nucleus of the lateral lemniscus.

►Cochlear Nucleus

Ocular Abduction

Definition
Horizontal movement of the eye away from the nose.

Ocular Counter-rolling Response

Definition
Conter-rotation of the eyes about the optic axis, i.e., torsion, during an imposed head or body tilt to the right or to the left about the naso-occipital axis (see also "VOR-tilt VOR").

►Vestibulo-Oculomotor Connections
►Vestibulo-Oculomotor System: Functional Aspects

Ocular Dominance

Definition
The degree to which one eye dominates a given neuron in the visual pathway or the perception of a scene.

►Binocular Vision

Ocular Drift Movements

Definition

Involuntary, smooth, and mostly slow, eye movements that do not correspond to a target movement. Some types of drift occur predictably in certain behavioral contexts such as: glissades in the aftermath of saccades, anticipatory drift in the direction of an imminent target movement, centripetal drift during the attempt to maintain an eccentric eye position in darkness. Others are predominantly random such as the miniature drifts during fixation with velocities of the order of 0.1°/ s which can cause deviations from the intended fixation point of up to 0.2°, or the slow wanderings of the eyes during drowsiness which result in considerably larger excursions.

►Oculomotor Control
►Saccade, Saccadic Eye Movements

Ocular Following Responses (OFR)

Definition

Smooth eye movement elicited by optic flow from relative motion between observer and visual scene (or parts thereof) in a highly automatic manner (unconscious reaction, no instruction required) and at short latency (70–80 ms). It often is initiated by a series of brief acceleration peaks creating a mean acceleration of up to 100°/s^2; considerably larger values are achieved in the aftermath of saccades, though. OFR is considered to be part of the early or direct component of the optokinetic reflex.

►Oculomotor Control

Ocular Micromovements

Definition

Involuntary movements occurring during fixation consisting of (i) tremor, (ii) slow drifts and (iii) microsaccades. Tremor and drifts are uncorrelated in the two eyes whereas microsaccades have the same direction and similar – though not identical -amplitudes in both eyes. As a result of these micromovements, the line of sight describes an erratic, two-dimensional path about the intended fixation point.

►Oculomotor Control
►Saccade, Saccadic Eye Movements

Ocular Motoneurons

Motoneurons that innervate the ocular muscles.

►Evolution of Oculomotor System

Ocular Muscles

Muscles that move the eye in the orbit.

►Evolution of Oculomotor System

Ocular Tremor

Definition

Involuntary ocular micromovement occurring during fixation and consisting of waxing and waning irregular oscillations with frequencies between 70 and 90 Hz and mean amplitudes of about 0.002°.

►Oculomotor Control

Oculocentric Frame of Reference

Definition

Also, “Retinotopic frame of reference.” A frame of reference centered on the eyes and moving with them.

►Eye Movements Field

Oculo-manual Synergy

►Eye-Hand Coordination

Oculomotor

►Evolution of the Vestibular System

Oculomotor Cerebellum

Definition

Usually refers to the medial parts of the cerebellum that regulate the generation of saccadic and smooth-pursuit eye movements.

►Cerebellum, Role in Eye Movements
►Saccade, Saccadic Eye Movements
►Smooth Pursuit Eye Movements

Oculomotor Control (Theory)

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Definition

The theory of oculomotor control aims at metaphorically understanding which types of innervation patterns are required to generate the various types of eye movements (►saccades, ►reflexive saccades, ►micro-saccades, ►express saccades, ►corrective saccades, ►pro-saccades, anti-saccades, ►catch-up saccades, smooth pursuit, vergence, fixation), and how afferent (mostly visual and vestibular) and efferent information is processed to shape these patterns (sensori-motor transformation). The metaphors it uses mostly draw on control systems theory and are referred to as models; typically, the modeling approach disregards the intricacies and variety of the neural substrates, lumping many of them into a small number of processing stages with either mathematically or empirically defined transfer characteristics between input and output. Processing stages interact by way of signals which can represent a flow of neural activity along axons or physical parameters such as position or velocity. Formerly, models had to be simple to be amenable to mathematical analysis, whereas nowadays the behavior of very complex structures can be rapidly determined by simulation software.

Characteristics

Description of the Theory

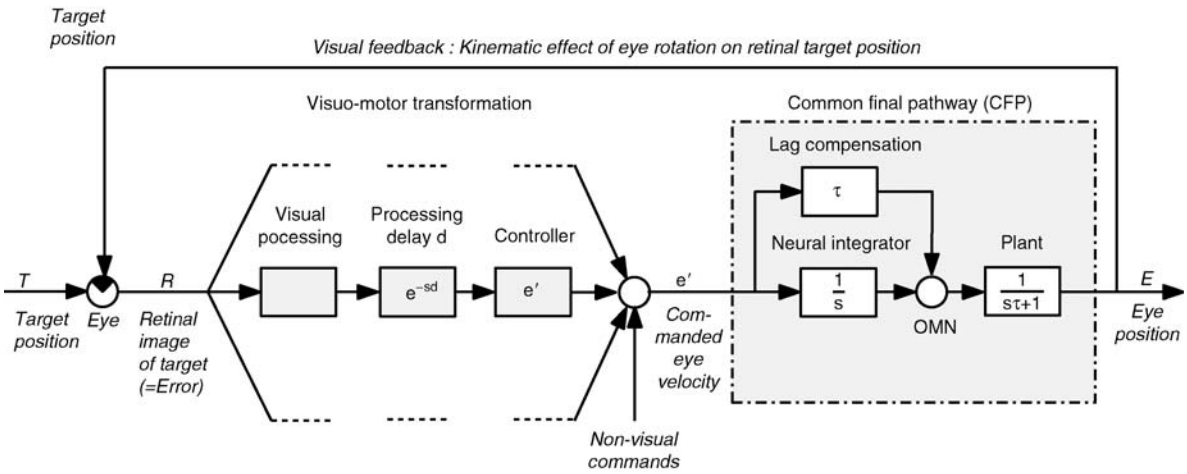
Common Characteristics of Visual Eye Movement Control

A prototypical scheme of visual eye movement control using a high level of abstraction is shown in Fig. 1. In particular, this and the following schemes do not explicitly show the bilateral symmetry of the oculomotor system and the elaborate push-pull interactions of its constituent elements; rather, they represent the net effect of these interactions.

Visually controlled eye movements aim at bringing the retinal image of visual target objects into the foveal area and at stabilizing them there. The basic information available to this end is *R,* the target's retinal eccentricity with respect to the fovea. *R* reflects the difference between target (*T*) and eye (*E*) position, and represents the current error in eye position; because of the "built-in" retroaction of *E* on *R*, that is, on the very signal it is reacting to, visual eye movement control constitutes a *negative feedback* system and is said to be *closed loop*. *R* is processed by a number of parallel, semi-independent pathways that perform the visuo-motor transformations required for the various types of visually controlled eye movements. In Fig. 1, these pathways are symbolized by dashed signal paths, while the typical structure of one of them is shown in more detail as a reference for the further description.

R first must be detected and processed by the visual system to obtain the information (e.g., error velocity) based on which the *controller* can generate an error-correcting motor command. Detection and processing of R, but also the operation of the controller and of other stages, require considerable time. These delays can be lumped into a single delay time (d) that represents the latency of the eye's response to a change of target position or velocity.

Interestingly, for all types of eye movements, including those controlled by non-visual signals (e.g., vestibular), the primordial motor commands issued by their respective controllers appear to specify *eye velocity* rather than eye position. In Fig. 1, these commands are shown to converge at a summing junction whose output represents a compound eye



Oculomotor Control (Theory). Figure 1 Basic structure of visual eye movement control. Italicized text and symbols denote *signals*; symbols beginning with lower case denote neural activity; upper case refers to physical quantities. Normal print describes functions and identifies the various elements of the scheme; symbols inside boxes describe global transfer characteristics of these elements by Laplace transforms (s, complex frequency; τ, time constant of plant).

velocity command (e'). This signal is converted into an eye position command by a stage that calculates its time integral. The substrate of this so-called *neural integrator* (NI) has been located to the medial vestibular nucleus and the nucleus prepositus hypoglossi and their reciprocal connections with the vestibulo-cerebellum. NI is also being referred to as *hold integrator* because it is responsible for holding the eyes at whatever position they have been brought to by a preceding, but now gone, e'-signal. NI has been the target of interesting attempts to explain integration in terms of a network of neurones that excite themselves via reciprocal connections to neighboring neurones [1].

The output of NI reaches the oculomotor nuclei (OMN); in the case of horizontal eye movements the abducens nucleus (nVI) in the first place, from whence it is forwarded to the rectus medialis complex of the contralateral oculomotor nucleus (nIII). OMN, in turn, send the position command to the extraocular eye muscles. The mechanical compound consisting of these muscles, the eye ball, and its connective tissue is collectively referred to as *plant*. The dynamics of the plant is dominated by visco-elastic forces, while the mass of the globe plays a minor role. As a first order approximation it can be described by a first order lag system with time constant $\tau = 150–200$ ms. Thus, a step increase of OMN activity causes the eye to exponentially approach the position coded by this step, with fairly sluggish creeping in the final phase. To overcome this sluggishness, there is a direct projection of e' to OMN, which adds a velocity component to the position command obtained from NI. This combination of position and velocity components becomes particularly clear during saccades, where a *pulse-step pattern* of innervation is observed in OMN.

Theoretically, if the gain of the direct projection assumes the numerical value of τ, the compound labeled "Common final pathway" in Fig. 1 behaves like an ideal integrator which accurately converts e' into eye position E, and for many purposes such a simplification is an acceptable approximation. The term *common final pathway* (CFP) for the aggregate consisting of NI, lag compensation, OMN, and plant reflects the belief that all velocity commands – visual and non-visual, saccadic and smooth – are processed by the same integrator and that their direct projections all converge at the same pool of motoneurones. This notion is a useful approximation for many purposes but should not be overvalued. Already at the level of the extraocular eye muscles, the occurrence of different types of muscle fibres raises the suspicion of a functional division according to, for example, fast and slow eye movements. Also, as yet there is no agreement as to how far ►vergence movements share the integrator for ►conjugate eye movements or use separate pathways.

Controllers

The oculomotor system's closed loop character combined with its considerable delay time ($d = 100–200$ ms) causes a major complication: If its response to a change of target position or velocity is to be accurate and fast (i.e., not much longer than d), the gain of its controller – essentially the ratio E/R – must be large. On the other hand, long delays combined with a large gain cause instability (oscillations) in a closed loop system. Different strategies have been developed by the saccadic

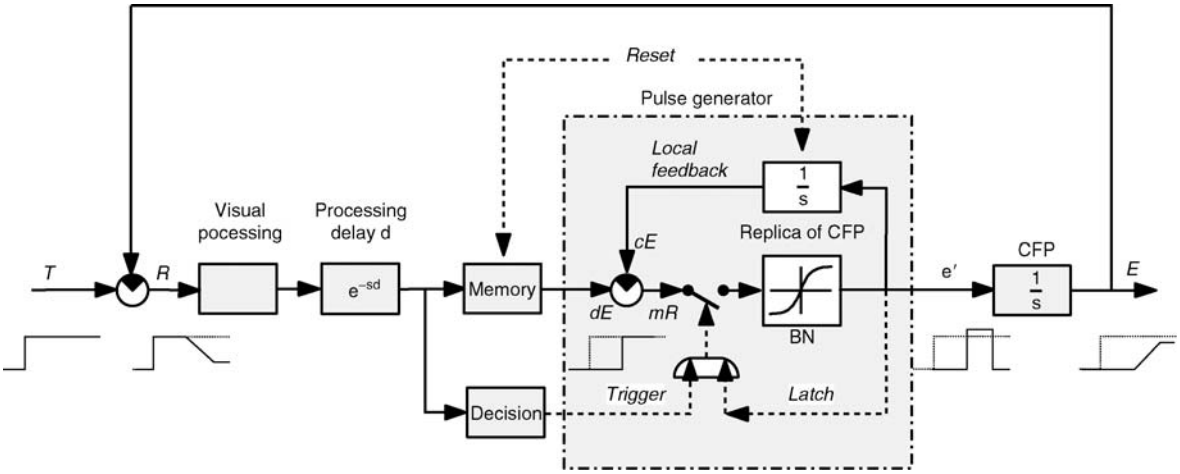
and smooth pursuit systems, to arrive at a viable compromise between response velocity and accuracy on the one side and stability on the other side.

Saccades

Basically, the control of saccades [2,3] (Fig. 2) can be likened to the operation of a sample-and-hold system: The error $R(t_0)$ existing at time t_0 is measured by the visual system and transferred to a memory and a decision stage. After a processing delay (d), the decision stage triggers a neural *pulse generator* which emits a high-amplitude, short-duration pulse of neural activity, whose mathematical integral approximately equals the value of $R(t_0)$ held in memory. Fed into CFP, this pulse acts as the saccadic velocity command e' and produces a fast, ramp-like movement of duration d_S – the saccade. At the end of this saccade, the sequence of events repeats: the now existing error $R(t_0 + d + d_S)$ is again visually measured and, if non-zero, corrected by a further saccade. In this way the execution proper of saccades is not visually controlled, but *open-loop* with respect to visual feedback. It is, however, thought to be under *local feedback* control: a copy of the e'-command sent to CFP would be fed into a neural replica of CFP – basically an integrator – whose output therefore images current eye displacement (*cE*) without incurring visual delays. Subtraction of *cE* from the *desired eye displacement* held in memory (*dE*) yields the current *motor error* (*mR*) which indicates how far the eye still has to go. If switch OPN is closed, *mR* drives a pool of burst neurones (BN, located in the vicinity of nIV and in the mesencephalon) which emit the e'-pulse. The pulse, therefore, would last until $mR = 0$ (implying $\int e'dt = dE$, as desired). BN activity would vary linearly with small *mR* but level off with large *mR*, thus determining the well-known non-linear relationship between saccade velocity and amplitude. Switch OPN provides for the discrete nature of saccades; to close it, a trigger impulse representing an "explicit" decision for a saccade is required, and in order to remain closed BN activity must entertain a "latch" signal. Therefore, as mR approaches zero and silences BN, the switch opens making the loop refractory for new motor errors until a new decision is issued. In the mean time, both the replica of CFP and the memory would be reset to zero (the former is often referred to as "*resettable integrator*"). A likely substrate of switch OPN are the omnipause neurones in the pontine raphe, which inhibit BN during fixation and are silenced before BN activity starts.

Closer experimental analysis of the saccadic system has revealed important features that are not covered by the basic scheme in Fig. 2 (i) The decision for a saccade and the desired amplitude (*dE*) put into memory are not necessarily based on the same sample $R(t_0)$; rather, *dE* reflects some kind of average of $R(t)$ from the interval $t_0 < t <$ d-80 ms. (ii) Processing of successive saccades does not always occur in a strictly serial manner but can considerably overlap in time. (iii) Saccades are not completely open loop but can to some degree be modulated by concurrent visual events. (iv) A local (i.e., non-visual) feedback signal also reaches the visual processing stage, where it anticipates the visual consequences of ongoing (and perhaps even of as yet only decided-upon) saccades before the visual afferents can signal the resulting change of *R*.

Two other aspects not dealt with by the scheme in Fig. 2 are (i) The co-ordination between the eyes and the



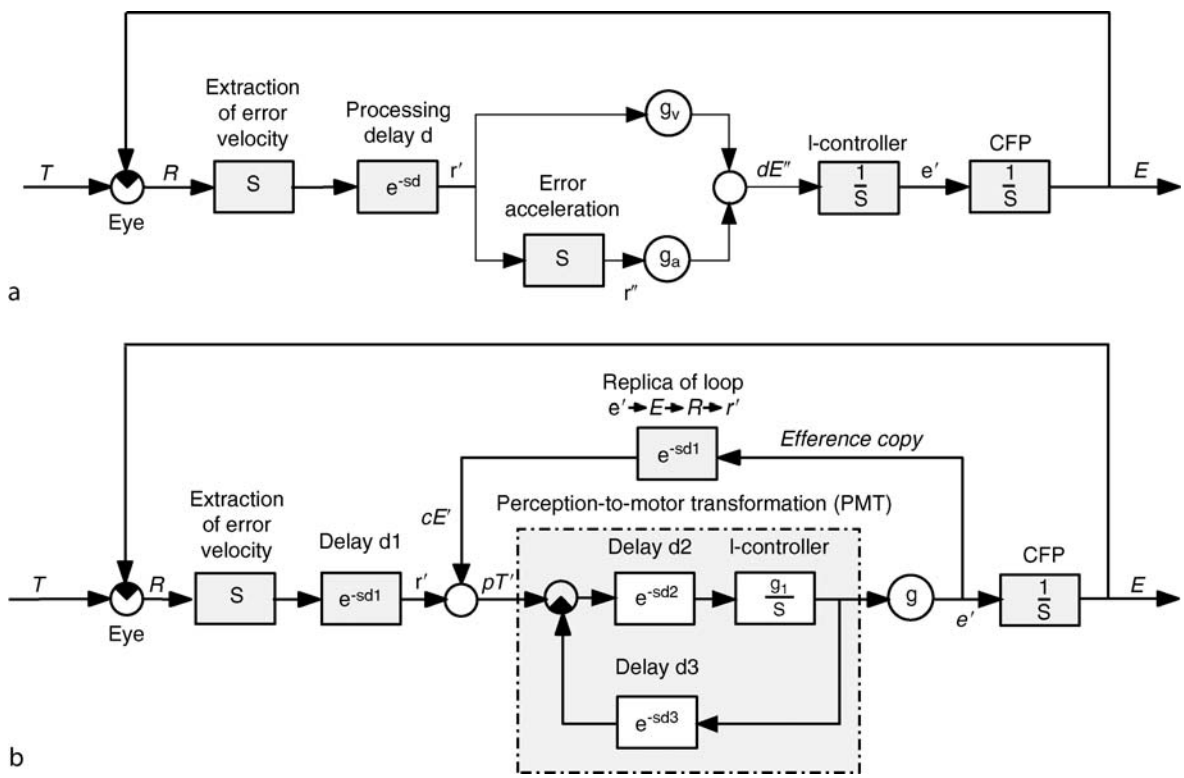
Oculomotor Control (Theory). Figure 2 Structure of saccadic eye movement control. *dE*, desired eye displacement; *cE*, copy of current eye displacement; *mR*, motor error; BN, burst neurones (icon sketches non-linear relation between motor error and magnitude of *e'*); OPN, switch disabling burst neurones during fixation; other symbols and conventions as in Fig. 1. *Insets* show time course of signals *T, R, dE, e'* and *E* in relation to a step of *T* (*dashed*).

head during natural gaze shifts, which are generally executed with the head moving in support of the eyes; several expansions and variations of the basic structure have been proposed in which vestibular mechanisms play a crucial role for this co-ordination [4]. (ii) Whereas small displacements in 2D-space can be essentially accounted for by two orthogonal systems of the type sketched in Fig. 2, the laws of spherical geometry require that not only R but also E be taken into account when creating the e'-signal for large displacements between arbitrary positions.

Smooth Pursuit Eye Movements (SPEM)

Basically, two alternative control structures are being discussed to account for the experimentally observed characteristics of SPEM [5] (Fig. 3). The *error-driven model* (also called *image motion model* or *closed-loop model*; Fig. 3a) posits that the motor output is driven exclusively by the current error in the way implied by Fig. 1. In accordance with SPEM's function of stabilizing the image of moving targets on the retina, first the current *error velocity* r' (*retinal slip* of target image) is extracted from R. A second differentiating stage also calculates error acceleration r''. Signals r' and r'' are then combined by weighted summation to obtain a signal representing the desired eye acceleration ($dE'' = g_v \cdot r' + g_a \cdot r''$) which in turn is converted, by integration in the controller proper, into the eye velocity command e' sent to CFP. The lumped effect of this processing is that $E'(t + d) = g_a \cdot R'(t) + g_v \cdot \int R'(t)dt$; therefore, it can be likened to that of a PI-controller with delay time d. Dependent on the relative weights of the proportional and the integrating contributions, such a system can oscillate at frequencies from 0.5/d ($g_v = 0$) to 0.25/d ($g_a = 0$); given d = 0.1 s, this corresponds to the range 2.5–5 Hz. The SPEM responses of man to sudden target movements indeed exhibit damped oscillations of 3.8 Hz; yet, there is no combination of g_v and g_a that would account at the same time for this frequency and other essential features of SPEM responses (e.g., rise time, steady state accuracy, and dependence on target velocity). For a satisfactory explanation of all relevant SPEM characteristics, several non-linear gain elements (saturating with increasing input) have to be inserted into the pathways preceding the I-controller of Fig. 3a.

The alternative approach, the *perceived velocity* (or *open- loop*) model (Fig. 3b), tries to reconcile the various characteristics of SPEM by assuming that SPEM oscillations are caused by an "inner," local feedback loop rather than by the "outer," visual loop.



Oculomotor Control (Theory). Figure 3 Smooth pursuit control: (a) error-driven model; (b), perceived velocity model. Conventions as in Fig. 1. r' (r'') error velocity (acceleration); dE'', desired eye acceleration; cE', delayed copy of eye velocity; pT', perceived target velocity; g, gain coefficients. Other symbols as in Fig. 1.

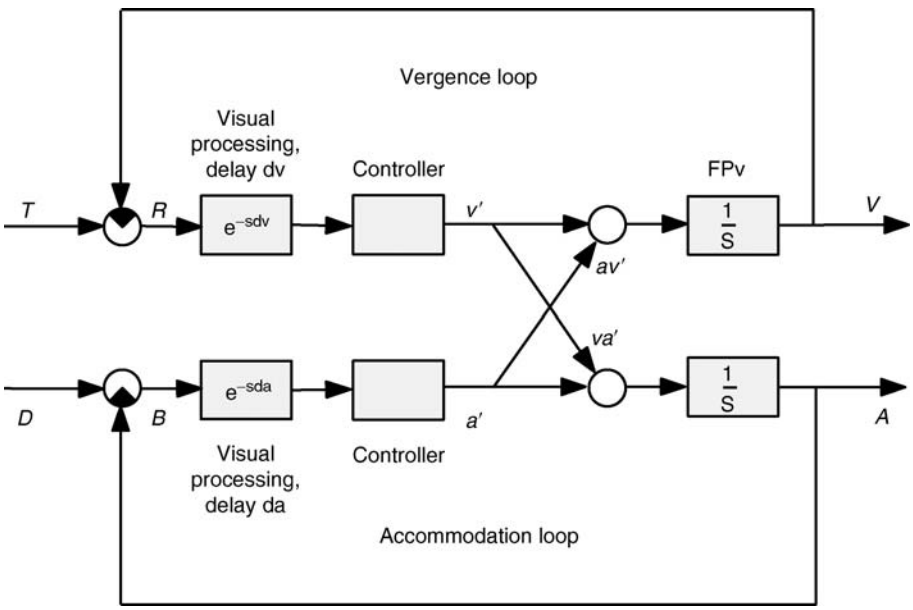
The model posits that the target's velocity, as it existed one visual delay time (d1) earlier, i.e., T'(t-d1), is *reconstructed* using delayed neural representations of (i) the retinal slip: $r' = R'$(t-d1), and of (ii) eye velocity: $cE' = E'$(t-d1); their sum, $pT' = T'$(t-d1), represents the "perception" of T' by the SPEM-system and may also determine conscious perception of target velocity. cE' would be obtained from an efference copy of the velocity command e', passed through a neural replica of the pathway mediating the retroaction of e' upon r'; with the simplifying assumptions of Fig. 3, this replica reduces to delay d1 (since $1/s \cdot s = 1$). If perceived target velocity pT', is then translated one-to-one into the velocity command e', SPEM velocity will faithfully follow T' except for a delay. During steady state operation, the *perception-to-motor transformation* (PMT) stage, when envisioned as a local feedback loop with integrating controller, has indeed a gain of one. The fact that in most people tracking a target of constant speed SPEM is slightly slower than the target, can be accounted for by gain element g (e.g., $g \approx 0.9$); a value $g < 1$ also insures stable operation of the positive (or "regenerative") feedback loop through which the efference copy of e' entertains the perception of T'.

By adding cE' to r' a positive, non-visual loop is created which offsets the subtraction of E from T and, hence, functionally neutralizes the negative visual feedback around the outer loop. Thus, SPEM becomes a virtually open-loop, feed-forward response to target movement. Therefore, oscillations cannot arise from the system architecture as a whole, but only in its constituents; specifically, it has been suggested that the experimentally observed damped oscillations arise in the inner (PMT-) loop, with frequency determined by delay times d2 and d3, and amplitude by integrator gain g_I. However, to render all relevant characteristics of SPEM, the perceived velocity model also requires the addition of non-linearities. Furthermore, proponents of the closed loop model point out that it has difficulties in rendering the effects observed during artificial prolongations of the delay time.

Both models apply only to the pursuit of targets moving at constant speed. With periodically moving targets, very effective predictive mechanisms dominate behavior which can virtually eliminate the delay between target and eye and, therefore, require more sophisticated models.

Vergence Movements

The control of vergence movements (Fig. 4) differs from that of saccades and SPEM in several aspects: It must move the two eyes in opposite directions and it is not only driven by errors in eye position or velocity (here: by retinal disparity) but also by an input unrelated



Oculomotor Control (Theory). Figure 4 Structure of vergence control. T, convergence called for by target; R, retinal disparity; v', commanded velocity of vergence; V, vergence angle of eyes; D, target distance^{-1} (diopters); B, error in accommodation (blur); a', commanded rate of change of accommodation; A, accommodation; av' and $va'A$, contributions of accommodation to vergence and vice versa (mostly denoted AC/A and CA/C in the literature); FPv, final pathway of vergence system (partially overlapping with CFP). Conventions as in Fig. 1. (For a broad synopsis of the use of models in oculomotor physiology see Carpenter RHS (1988) Movements of the eyes (2nd edition). Pion, London For examples of how models benefit the analysis of neuro-ophthalomological problems see Leigh RJ, Zee DS (1999) The Neurology of Eye Movements (3rd edition). Oxford University Press, New York, Oxford).

to eye position, namely the error in accommodation (retinal blur); the response to this input is known as *accommodative vergence*. As accommodation, in turn, is not only driven by blur but also by retinal disparity (*convergence accommodation*), two mutually coupled feedback circuits result with fairly similar constituent elements, except for a significantly larger delay (da) in the accommodative loop as compared to the vergence loop (dv). The situation is further complicated by the possibility that, much as with conjugate movements of the two eyes, there might be separate systems for pursuit vergence (tracking a target moving slowly in depth) and saccade-like vergence (called for by sudden changes of fusional demands) [6]; therefore, no details of the controller are specified in Fig. 4. As with other oculomotor subsystems, the controller signal reaches the plant both via a direct (velocity coding) and an integrating (position coding) pathway which, when lumped with the plant, could be roughly equated to an integrator (box FPv). Due to the disconjugate character of vergence, the integrating pathway cannot be identical to the neural integrator of the common final pathway (CFP) of conjugate movements, although it may partially overlap with it [7]; hence, the notion of a CFP is not applicable here in a strict sense. Finally, it is not clear whether the cross-coupling between vergence and accommodation occurs before the integration of the commanded vergence (v') and accommodation (a') velocities (as shown in Fig. 4), or thereafter [8].

References

1. Arnold DB, Robinson DA (1997) The oculomotor integrator: Testing of a neural network model. Exp Brain Res 113:57–74
2. Becker W (1989) Metrics. In: Wurtz RH, Goldberg ME (eds) The Neurobiology of Saccadic Eye Movements. Elsevier, Amsterdam, New York, Oxford, pp 13–67
3. Scudder CA, Kaneko CRS, Fuchs AF (2002) The brainstem burst generator for saccadic eye movements. A modern synthesis. Exp Brain Res 142: 439–462
4. Galiana HL, Guitton D (1992) Central organization and modeling of eye-head coordination during gaze shifts. Ann NY Acad Sci 656: 452–471
5. Churchland MM, Lisberger SG (2001) Experimental and computational analysis of monkey smooth pursuit eye movements. J Neurophysiol 86:741–759
6. Zee DS, Fitzgibbon EJ, Optican LM (1992) Saccade-vergence interactions in humans. J Neurophysiol 65:1624–1641
7. McConville K, Tomlinson RD, King WM, Paige G, Na EQ (1994) Eye position signals in the vestibular nuclei: Consequences for models of integrator function. J Vestib Res 4:391–400
8. Schor CM (1992) A dynamic model of cross-coupling between accommodation and convergence: Simulations of step and frequency responses. Optom Vis Sci 69:258–269

Oculomotor Dynamics

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Synonyms

Oculomotor plant; Orbital dynamics

Definition

►Oculomotor dynamics are the properties of the oculomotor system that determine the time-course of the rotation of the eye in response to the discharges of ocular motoneurons. These properties are a product of the inertia of the eye, the viscoelastic properties of the tissue surrounding the eye, and the dynamic properties of the extraocular muscles that control its movements. These properties are usually described mathematically using differential equations or their equivalent (e.g. computer models).

Characteristics

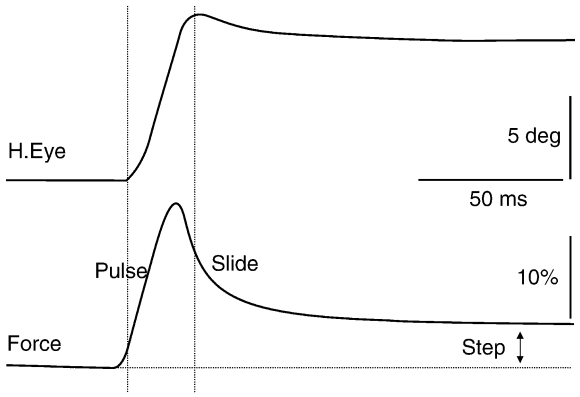
Measurement of Oculomotor Dynamics

The time course of an eye movement is not a replica of the aggregate discharge rate of the ocular motoneurons, but is modified by oculomotor dynamics. The difference between the two can be quantified and used to describe oculomotor dynamics. This measurement is a composite of the three factors listed above. To interpret this measurement, it is also important to directly measure inertia, tissue viscoelasticity, or muscle properties in isolation using mechanical methods, as described below. Force transducers placed in series with the extraocular muscles have also helped to isolate the dynamics due to the muscles and the dynamics due to the eye and orbit [1,2].

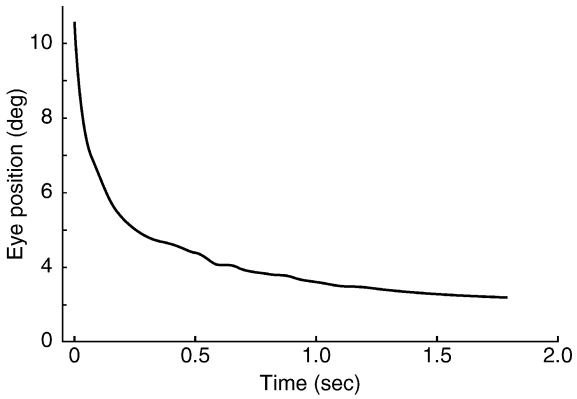
The force produced during the generation of a saccade is illustrated in Fig. 1. The time course is divided into three components; the "pulse" that occurs during the saccade, the "slide" (decay in force) occurring after the end of the saccade, and the "step" (long-term force) that keeps the eye in a static position until the next eye movement.

Viscoelastic Properties of the Orbital Tissue

Rotation of the eye causes a displacement of the orbital tissue, such as the conjunctivum, Tenon's capsule, fat in the orbit, and the connective tissue of the extraocular muscles. These tissues resist rotation, their resistance displaying both an elastic and a viscous component. The elastic component provides a static restoring force that depends only on the angle of rotation away from straight ahead. This force increases with angular deviation nearly linearly over a range of angles, but



Oculomotor Dynamics. Figure 1 Recording of the horizontal eye position (H. Eye) and muscle tension (Force) in the lateral rectus muscle recorded during an abducting horizontal saccade. Tension increases slightly before saccade onset and peaks somewhat before saccade termination. This phase is frequently called the "pulse" of force because of the waveshape of the associated motoneuron discharge, and is responsible for producing the rapid velocity of saccades. This is followed by an initially rapid and then slow decline in force commonly called the "slide." Normally the eye would be stationary during this time, but the force transducer has caused a minor abnormality. Force never declines to its initial value, but rather, there is a persistent force (the "step") that holds the eye in its final abducted position. Force is expressed as a percentage of the maximum force developed by the muscle during any saccade, probably 50–60 g-force. Dotted lines mark saccade onset and termination. Figure modified from Miller & Robins, Fig. 9 [2].



Oculomotor Dynamics. Figure 2 The return of eye position towards straight-ahead gaze after being released from an abducted position. Movement is initially very rapid, then slows down, and finally creeps toward a final position over several seconds (not shown). Data is replotted from Sklavos et al. [4].

increases more rapidly after about halfway to the maximum of natural eye movements (see ►Orbital mechanics). The viscous component resists an ongoing rotation of the eye with a force that is proportional to the velocity of rotation.

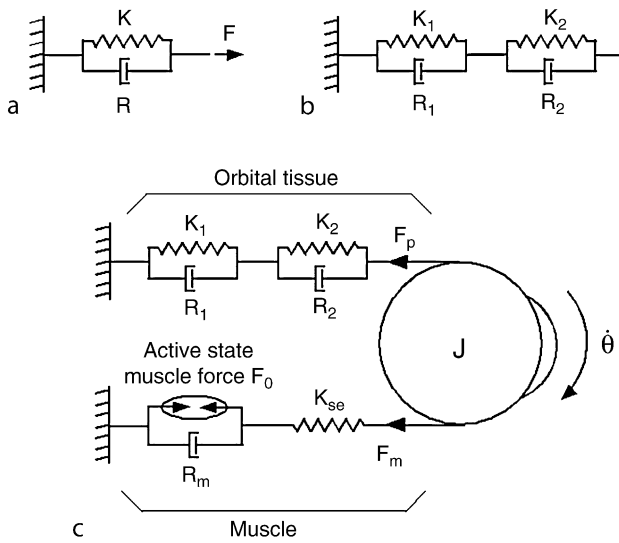
The mechanical method of measuring the viscoelastic forces is to pull on the eye with a constant tangential force, and measure the time course of the change in angular position. The eye rotates rapidly during the first few milliseconds, but progressively slows down and continues to move increasingly slowly over succeeding seconds. The process is characteristic of most tissue in the body and is known as "tissue creep" [3]. An equivalent experiment is illustrated in Fig. 2, where the eye is held in a static position and then released (isotonic force = 0). The eye rotates back towards straight ahead as described above. Technically, the change in position is described by the sum of an infinite number of exponentials with different ►time constants [3], but practically, a very good fit to the data can be obtained with a small number of exponentials. For the data in Fig. 1, one exponential accounts for 85% of the variance, two account for 98.5%, and four account for 99.9% [4].

For a quantitative description of the viscoelastic properties of the orbit, each exponential is modeled as the product of one "Voigt element," which is a spring (the elastic component with spring constant K) in parallel with a dashpot (the viscous element with viscosity R) as in Fig. 3a. Two exponentials are modeled as two Voigt elements in series, as in Fig. 3b.

Using a single Voigt element to describe oculomotor dynamics [5] has intuitive appeal because it requires a neural controller for eye movements having only two components. One is a velocity command, such as the burst of saccadic burst neurons (see ►MLBNs) or the discharge of vestibular afferents during the ►vestibuloocular reflex (►VOR) that is needed to overcome the viscosity of the orbital tissue. The second is a position command, thought to be obtained by integrating the velocity command (see ►Neural integrator), that is needed to overcome the elasticity of the tissue. However, this model cannot explain the presence of the slide (Fig. 1) or the frequency-dependent characteristics of motoneuron firing-rate modulation during sinusoidal ►smooth pursuit [6], and predicts an unrealistically high force to move the eye during a saccade [6]. Using two Voigt elements (Fig. 3b) greatly reduces all three problems, and is quite adequate for the didactic purposes of this article.

Muscle Dynamics

Force in the extraocular muscles varies with the number of motoneurons recruited and the firing rate of each motoneuron. Three factors contribute to the dynamics of force buildup (or decline) in the muscles; the "twitch



Oculomotor Dynamics. Figure 3 Components used in modeling oculomotor dynamics, including a nearly complete model. A single Voigt element (a) is composed of a spring with spring constant K (representing elastic restoring forces in the orbit) and a dashpot with viscosity R (representing the viscous, velocity dependent, properties of orbital tissue). A single Voigt element responds to a step change in force with a change in length fit by a single exponential having a time constant of R/K. The viscoelastic properties of the orbit are more accurately modeled by two (b) or more (not shown) Voigt elements in series. This model of the orbital tissue is shown attached to the eyeball (top of (c)), with a model of the muscle attached at the bottom. The parallel elastic component of the muscle has been lumped with the other orbital tissue. The active-state force generator (muscle crossbridges) is in parallel with a dashpot with viscosity R_m, which models the reduction in force F_m according to the ►force-velocity relationship. The series elastic component (spring constant K_{se}) lengthens during the initial buildup of force at the onset of a saccade. For all practical purposes, the inertia of the eye (moment J) can be ignored, meaning that the magnitude of $F_p \approx F_m$.

time" of the muscle, the distributed recruitment of motoneurons over time, and the firing rate of the active motoneurons. These factors make little difference during slow eye movements (smooth pursuit, VOR), but a major one during rapid saccadic eye movements [6].

An action potential in a motoneuron and the muscle fibers it innervates produces a rapid buildup to a peak of force and then a gradual decline. The time to peak is called the "twitch time" [7], and is 5–7 ms in monkeys [8]. The finite twitch time is due to the fact that connective tissue and muscle proteins are springy (series elastic component [7]) in combination with the fact that rapidly shortening muscle develops less force (►Force velocity relationship [7]; see ►Muscle twitch).

During the repetitive firing of a motoneuron, the force of each twitch adds to the force that remains from the preceding twitches. At the start of repetitive firing, this superposition produces a cumulative force that builds up and saturates with a roughly exponential envelope whose ►time constant decreases as the firing rate increases [9]. During an actual saccade, there is a complex interplay between the ►extraocular motoneuron firing rates and the force-velocity and length-tension properties of the shortening muscle, which makes exact modeling difficult. In practice, it has proven satisfactory to approximate all these dynamics as a single spring and dashpot in series and parallel, respectively, with the active (force-producing) components of the muscle (F_o in Fig. 3c).

The bursts of repetitive firing in extraocular motoneurons occurring just prior to saccades do not start simultaneously, but their onsets are spread over 6–8 ms in monkeys [5,9] and could be longer in humans, who have slower saccades. The effect of this distributed recruitment is to slow the initial acceleration of the eye during saccades.

Inertia of the Eye

Calculations, modeling, and measurement all show that the force required to overcome the inertia of the eye is negligible during slow eye movements and is very small during saccades [6,10]. For all practical purposes, inertia can be ignored in models of oculomotor dynamics. However, the inclusion of an unrealistically high moment of inertia has been used in some modeling studies [11] to account for the discrepancy between the slow acceleration of the eye relative to the almost instant buildup of firing rate in single saccadic burst neurons (see ►Burst cells – medium lead). This discrepancy, however, is the product of finite twitch times in the extraocular

muscles and the spread of burst-neuron and motoneuron recruitment times in relation to saccade onset, with a minimal contribution from the inertia of the eye.

Cumulative Orbital Dynamics

A model of oculomotor dynamics is illustrated in Fig. 3c. The viscoelastic properties of the orbital tissue are illustrated at the top of the eye, and the muscle is illustrated at the bottom. The agonist and antagonist muscles, which are reciprocally innervated and have mirror-image force profiles [2], have been lumped together into one muscle. The "parallel elastic component" of the muscle, which is sometimes modeled as a separate element, has been lumped into the orbital tissue. This is consistent with the fact that the passive muscle has viscous as well as elastic properties that are measured with the other orbital tissues in the release experiments described above [4,10]. The moment of inertia is denoted as J. Treating J as negligible, the differential equation describing eye acceleration as a function of muscle force (F_m), rate of change of force, and the viscoelastic impedance is below:

$$\ddot{\theta} = \frac{1}{\mu}\left(F_m + T_s\dot{F}_m - K_o\theta - R_o\dot{\theta}\right)$$

Ks, Rs, and Ts are composite spring, rate, and time constants [6,10]. Muscle force (F_m) is the active-state force (F_o) reduced by the rate of change of force and eye velocity:

$$F_m = F_o - T_m\dot{F}_m - R_m\dot{\theta}$$

Equations that include inertia can be found in Robinson [10]. Values for all parameters can be found in references [4,6,10].

The interaction of all the dynamic elements will be illustrated for a saccade. To begin the saccade, motoneurons begin their bursts over a range of times leading to a gradual buildup in active-state tension. The buildup of force delivered to the eyeball (F_m) is further slowed by the dynamic properties of the muscle, as discussed above. This buildup is illustrated in Fig. 1 during the so-called "pulse" phase. Shortly after the onset of force, the eye begins to rotate. As the inertia of the eye is small, F_p is almost equal to F_m, reflecting that the primary impedance to motion is provided by the viscoelastic properties of the orbital tissue. At the end of the pulse, motoneuron firing rate drops rapidly at first, and then more gradually with a "slide" similar to that illustrated in the force trace of Fig. 1. In a normal eye (without a force transducer), the eye would stop moving at this point. The decline in muscle force compensates for the decline in the reactive force in the orbital tissues as they "creep" to a new steady state. In terms of the model in Fig. 3, the Voigt element with the faster time constant was initially stretched disproportionately, and relaxes during the slide as the Voigt element with the slower time constant stretches. At the end of the slide, which can take several seconds in the actual eye or a model with more than two Voigt elements, there is a residual force (the "step" in Fig. 1) that is needed to maintain the eye at its new position against the just stretched elastic components of the orbital tissue.

References

1. Collins CC, O'Meara D, Scott AB (1975) Muscle tension during unrestricted human eye movements. J Physiol (London) 245:351–369
2. Miller JM, Robins D (1992) Exraocular muscle forces in alert monkey. Vis Res 32:1099–1113
3. Fung YC (1993) Biomechanics; mechanical properties of living tissues. Springer-Verlag, New York
4. Sklavos S, Porrill J, Kaneko CRS, Dean P (2005) Evidence for wide range of time scales in oculomotor plant dynamics: implications for models of eye-movement control. Vis Res 45:1525–1542
5. Robinson DA (1970) Oculomotor unit behavior in the monkey. J Neurophysiol 33:393–404
6. Fuchs AF, Scudder CA, Kaneko CRS (1988) Discharge patterns and recruitment order of identified motoneurons and internuclear neurons in the monkey abducens nucleus. J Neurophysiol 60:1874–1895
7. Aidley DJ (1998) The physiology of excitable cells. Cambridge University Press, Cambridge
8. Fuchs AF, Luschei ES (1971) Development of isometric tension in simian extraocular muscle. J Physiol (London) 219:155–166
9. Fuchs AF, Luschei ES (1970) Firing patterns of abducens neurons of alert monkeys in relationship to horizontal eye movement. J Neurophysiol 33:382–392
10. Robinson DA (1964) The mechanics of human saccadic eye movement. J Physiol (London) 174:245–264
11. van Gisbergen JAM, Robinson DA, Gielen S (1981) A quantitative analysis of generation of saccadic eye movements by burst neurons. J Neurophysiol 45:417–442

Oculomotor Nerve (III)

Synonyms

N. oculomotorius (N.III)

Definition

The oculomotor nerve is a motor cranial nerve endowed with both somato- and visceromotor components, for which one complex is responsible in each case. Together with the trochlear nerve (IV) and abducens nerve (VI) it controls eye movements.

It is involved in the lateral and medial eyeball movements (lateral rectus muscle and superior oblique muscle), raising of the palpebra as well as accommodation (ciliary muscle) and adaptation (sphincter muscle of pupil). Skull: superior orbital fissure.

►Nerves

Oculomotor Nucleus

Definition

A nucleus which contains both motoneurons and interneurons. The motoneurons send direct projections to all extraocular muscles except for the superior oblique muscle and the lateral rectus muscle.

Oculomotor Plant

►Eye Orbital Mechanics
►Oculomotor Dynamics

Oculomotor Systems

►Evolution of Oculomotor System

Oculomotor Vermis

Definition

The circumscribed portion of the cerebellar vermis (lobules VIc and VII) that appears to be integral to the control of saccadic and smooth-pursuit eye movements. The time course of changes in eye position or the firing rate of neurons can sometimes be described mathematically by an exponential, $X = X_0e^{-(t/T)}$, where X is the position or firing rate, X_0 is the initial value of X, t is time, and T is the "time constant" of the exponential. The time constant is equivalent to the amount of time required for X to decay to 36% (1/e) of X_0.

►Cerebellum, Role in Eye Movements
►Saccade, Saccadic Eye Movements
►Smooth Pursuit Eye Movements

Odor

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Synonyms

Odor; Odorant; Olfactory cue; Smell; Scent, Aroma

Definition

"Odor" refers to an emanation composed of multiple different odor molecules termed odorants, whose individual chemical properties are perceived by the sense of smell. In humans, this term is frequently used to describe a sensation as a result of odor perception, for example the pleasure resulting from the floral smell of roses (good odor) or the disgust following the smell of spoiled food (bad odor).

Characteristics

In contrast to the senses of vision, hearing and touch, the chemical senses - smell (and taste) - are challenged by an enormous number of molecularly distinct stimuli. Natural odors derived from food and plants and social stimuli, such as those present in urine, sweat and saliva, represent complex mixtures that contain a multitude of chemically diverse compounds. The information contained in these molecules is detected and processed by the sense of smell, a sensory modality that emerged very early in the evolution of living forms. Detection of olfactory cues is initiated by interaction of odor molecules with specific receptors located in the cellular membrane of olfactory sensory neurons in the nasal epithelium. The initial chemical odor information is then translated into neuronal activity patterns and subsequently converted into perceived odor quality and behavioral responses as a result of pattern recognition and evaluation by the brain.

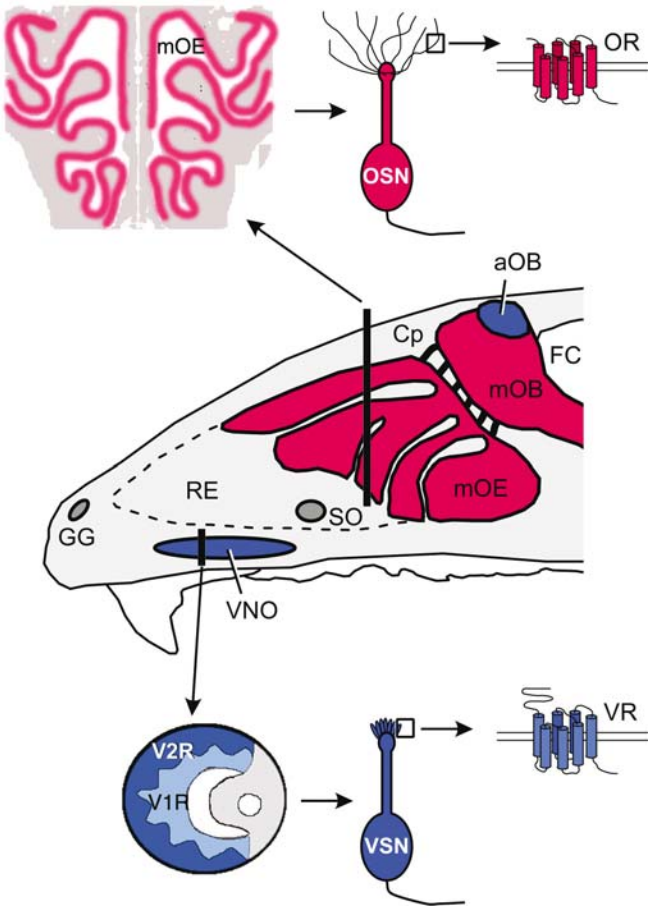
Odor Detection in Mammals Occurs Through Multiple Olfactory Subsystems

In vertebrates, the cellular, molecular and genetic mechanisms underlying odor detection and the sense

of smell are probably best understood in the mouse olfactory system. Odor detection begins in the olfactory sensory neurons (OSNs) located in the main olfactory epithelium (mOE) of the nasal cavity. Volatile odor molecules enter the nasal cavity with each breath and dissolve in the mucus covering the epithelial surface, a process that may be facilitated by small carrier molecules or odor binding proteins. The next step is a direct contact of odor molecules with the olfactory cilia which emanate from the dendritic knob of each OSN (Fig. 1).

These cilia contain all the necessary components for odor detection and subsequent chemo-electrical signal transduction. The electrical output signal produced by each OSN travels along a single axonal projection toward the main olfactory bulb (mOB) in the forebrain, the first relay station of odor processing in the brain. The axons from several millions of OSNs coalesce to form the olfactory nerve, also known as 1st cranial nerve.

In addition to a main olfactory system, most mammals have evolved an accessory olfactory (or vomeronasal) system (Fig. 1), which is anatomically and functionally distinct from the main system. Odor detection in the accessory olfactory system begins in the paired vomeronasal organ (VNO), located ventrally at the base of the nasal septum and rostral to the mOE. Odor stimuli are actively transported into the lumen of the VNO by a vascular pumping mechanism. The sensory epithelium of the VNO covers the inner medial side of each tube and, in analogy to the mOE, contains vomeronasal sensory



Odor. Figure 1 Schematic of a hemisected head of a mouse (sagittal view) illustrating the anatomical location of different olfactory subsystems and key structures. *Cp* cibriform plate; *FC* frontal cortex; *GG* Grüneberg ganglion; *mOB* main olfactory bulb; *RE* respiratory epithelium; *SO* septal organ of Masera; The black bar in the main olfactory epithelium (mOE, red) refers to the coronal section at the top left (arrow) that depicts the bilateral symmetry of the mOE. Olfactory sensory neurons (OSNs, red) contain numerous cilia that carry odor receptors (OR, red) of the GPCR type. The black bar in the vomeronasal organ (VNO, blue) refers to the coronal section shown at the bottom left with V1Rs and V2Rs expressed in the apical (light blue) and basal (dark blue) halves of the vomeronasal sensory epithelium, respectively. Vomeronasal neurons (VSN, blue) carry numerous microvilli that express vomeronasal receptors (VR, blue) of the GPCR type.

neurons (VSNs). These extend microvilli instead of cilia towards the lumen of the VNO. VSN axons project to the accessory olfactory bulb (aOB) located posterior and dorsal to the mOB (Fig. 1).

The traditional distinction that the mammalian main olfactory system recognizes general odor molecules and the vomeronasal system detects pheromones is no longer valid. The emerging picture is that both systems have considerable overlap in terms of the chemosignals they detect and the effects that they mediate [1]. Other, functionally less well characterized olfactory subsystems in rodents comprise of the septal organ of Masera and the Gruneberg ganglion (Fig. 1). Finally, some odor molecules such as menthol and phenylethyl alcohol can be detected by free nerve endings of the 5th cranial nerve which are part the somatosensory system. These nerves are often sensitive to pain as well as temperature stimuli and terminate in the nasal cavity.

Odor Molecules

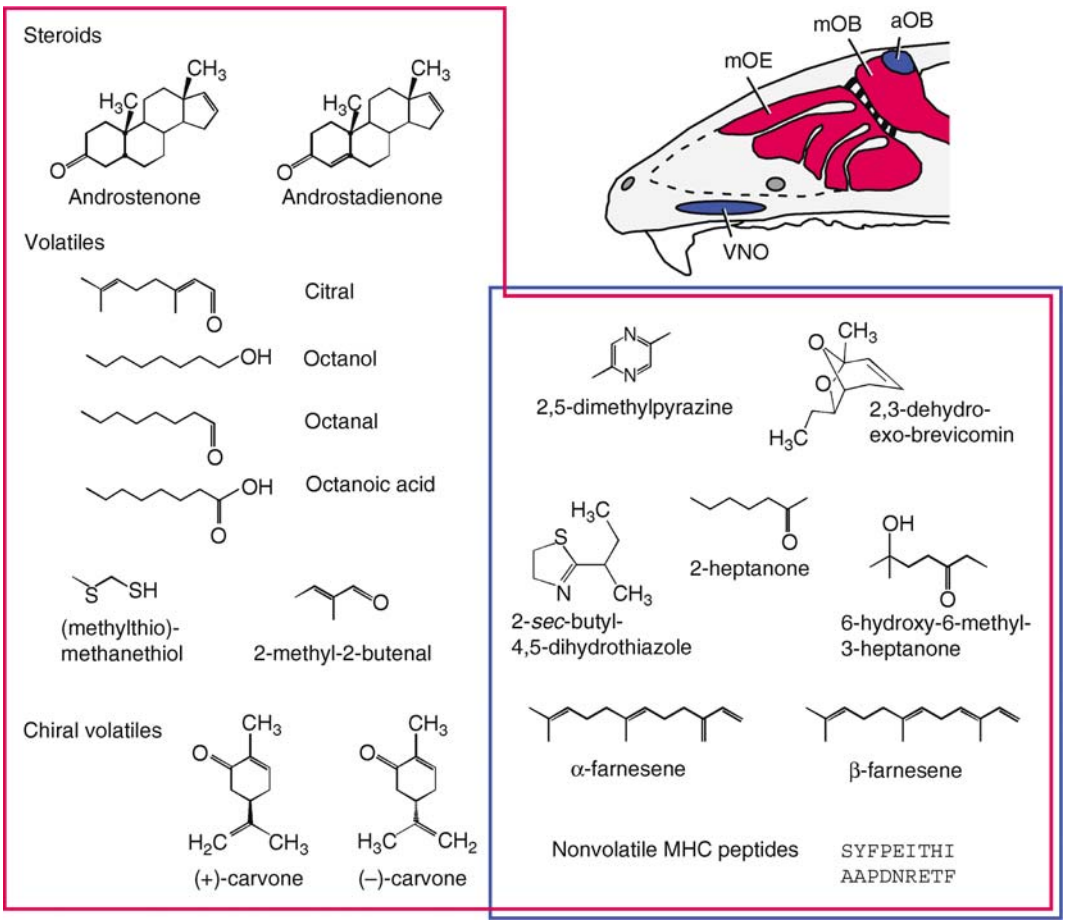
The olfactory environment is estimated to comprise hundreds of thousands of structurally distinct compounds that potentially can be detected and discriminated by the olfactory system. These odor molecules are classified by several means, most commonly by the presence of specific physical and chemical properties or encoded odor quality, but also by the characteristics of the corresponding receptors, resulting activity patterns in the brain, and function. Typical odor molecules of air-breathing species are small hydrophobic chemicals of organic origin with a molecular weight of less than 300 Da, i.e., they are volatile at ambient temperature. In aquatic animals, requirements for odor molecules are different, with non-volatile, hydrophilic compounds like amino acids being among the best odor ligands identified. Chemically, odor molecules differ by many parameters including size, functional groups, 3D-structure, and flexibility. They encompass the whole array of aliphatic acids, alcohols, aldehydes, ketones, and esters. To the human nose, changes of functional groups can cause pronounced differences in perceived odor quality, e.g., octanoic acid has the smell of sweat whereas the structurally related aldehyde octanal (Fig. 2) has the smell of oranges. The presence of functional groups is not always a prerequisite for odor. Alkenes such as 2,4,4-trimethylpentane and cyclooctane both have pronounced camphor quality as a consequence of molecular shape.

Further chemical features that are subject to olfactory discrimination include differences in carbon bond branching and saturation, as well as substitutions by aromatic, alicyclic, polycyclic, and heterocyclic ring structures or halogens in numerous possible positions. For some substances, substitutions can be exchanged without altering odor quality, e.g., exchanging the aldehyde group in benzaldehyde with other groups of similar size and charge does not affect its bitter almond quality. Most intriguingly, humans are capable to distinguish between the enantiomers of chiral odor molecules, such as (+)-carvone (caraway) and (−)-carvone (spearmint), which is likely mediated by stereo-selective receptors (Fig. 2). Enantio-selectivity is also exemplified by the pheromonal compound androstenone that induces mating stance in female pigs. (+)-Androstenone (Fig. 2) has an unpleasant (sweat, urine) odor quality to some humans and a pleasant (floral, sweet) odor quality to others, while (−)-androstenone is generally perceived as odorless. In contrast to mice, enantio-selectivity in humans is less pronounced and restricted to few odor molecules, while most enantiomers encode identical odor quality. Furthermore, carvone and androstenone are typical examples for which specific anosmias - the inability to detect particular odor molecules - have been identified in a certain percentage of humans.

Odor Receptors

How is the neural recognition of this almost infinite number of structurally diverse odor molecules achieved? Early on it has been noted that for a molecule to have an odor it needs to possess a molecular configuration that is complementary to specific sites of its receptor system [2]. This stereospecific theory has been validated by the discovery of a multi-gene family encoding odor receptors (ORs) [3], a finding that has set a milestone in the molecular understanding of odor detection (http://nobelprize.org/medicine/laureates/2004/press.html). ORs belong to the superfamily of G-protein coupled seven-transmembrane domain receptors (GPCR) (Fig. 1), and are similar in structure to the rhodopsin and β-adrenergic receptors. The ability of the olfactory system to recognize thousands of different odor molecules derives from the large size and diversity of the OR family. Based on genome sequencing projects (http://www.ncbi.nlm.nih.gov/Genbank), more than 1,000 potentially functional OR genes have been identified in mouse, while humans are left with about 400 potentially functional OR genes. Phylogenetically, ORs are preserved from fish to mammals and divide into two major classes. Class-1 or fish-like ORs are encoded by aquatic animals detecting water-soluble molecules, but are also present in ~10% of the mouse gene repertoire. Class-2 ORs are unique to terrestrial vertebrates detecting volatile odors.

ORs are highly divergent, especially in transmembrane domains 3–5. As a result of multiple OR sequence alignments across species and the developing of computational prediction models, odor binding is envisioned to occur in a binding pocket formed by the OR. Specific amino acid residues in key positions, predominantly located in the highly variable transmembrane domains are thought to interact with different parts of the odor molecules. However, exactly which parts of



Odor. Figure 2 Chemical structure of odor molecules detected by the main olfactory epithelium (mOE) and the vomeronasal organ (VNO, blue). Steroids, volatiles including chiral volatiles and nonvolatile MHC peptides are detected by the mOE (red box). Overlapping odor cues that are detected by the mOE and the VNO encompass volatiles as well as nonvolatile MHC peptides (overlayed red and blue boxes). The main olfactory bulb (mOB, red) receives odor information from the mOE and the accessory olfactory bulb (aOB, blue) from the VNO.

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the odor molecules are recognized by the ORs is still subject to intense investigation.

In situ hybridization studies show that expression of ORs in the rodent mOE is organized in a zonal pattern and that each individual OSN expresses only one OR. OSNs that express the same OR are confined to one out of four rostro-caudal zones and axonal projections of homologous OSNs coalesce into two glomeruli (one lateral and one medial) in each mOB.

Odor Coding: Molecular Level

Despite the large size and diversity of the OR family, the question arises how a limited number of ~1,000 different ORs is capable of detecting an exceedingly larger variety of environmental olfactory cues? Identification of the first functional OR–odor ligand pairs [4,5], a process known as the "deorphanizing" of an OR, has solved this apparent discrepancy. Functional recordings of physiological odor reponses and polymerase chain reaction analyses of single OSNs have revealed that the discriminatory power of the olfactory system depends on combinatorial receptor activation as a result of an unusually broad ligand-tuning of individual ORs. Given that single OSNs express only a single OR-type, different odor molecules activate specific, partially overlapping sets of OSNs with distinct sensitivities. In other words, a single OSN has a receptive field composed of different odor ligands that bind its OR with distinct affinity. The fact that ORs detecting the same ligands can be both highly homologous or extremly divergent suggests that these ORs recognize identical or different odotopes (i.e., functional groups of an odor molecule), respectively. The resulting neural activity patterns are thus concentration-dependent: OSNs expressing ORs with the lowest threshold for a given odor are activated first, and the less sensitive ones

are recruited at higher concentrations. This concentration dependence may explain the psychophysical phenomenon that some odor molecules are perceived differently at different concentrations. For example, with increasing concentration the perception of indole by humans ranges from "flowery" to "fecal."

Chemical Properties of Odor Molecules

Despite the relatively small number of ORs that have been deorphanized thus far, several features underlying odor recognition have emerged. The receptive field of a given OR appears to be determined by the functional groups, structure, and flexibility of an odor ligand. Some ORs accept 2–3 functional groups such as aldehydes, alcohols, and aliphatic acids [5] in combination with 3–4 consecutive carbons, while other ORs appear to be restricted to single functional groups. For example, the rat I7 OR is activated by straight-chained aldehydes ranging from C7-C10, with octanal (Fig. 2) representing the best ligand identified thus far [4]. Unsaturated C-double bonds that confer molecular rigidity or carbon backbone branches are, depending on position, tolerated, but structurally related molecules with different functional groups, such as octanal and octanoic acid (Fig. 2), yield no receptor activation. Aldehydes are potent ligands with low detection thresholds, and more than 30 different octanal-responsive, yet unidentified rat ORs, have been estimated from octanal evoked activity patterns in the mOE. However, not all ORs exhibit such broad tuning and some receptors appear to be specialists for a single or very few odor molecules.

Ligand binding does not always induce receptor activation. Several studies show that odor molecules exhibit dual functions and are agonists for some ORs, but antagonists for others. Citral for example strongly reduces the response of OR-I7 to octanal (Fig. 2). Antagonistic effects of odor molecules add another level of complexity to olfactory coding and may coincide with the psychophysical observation that both perceived quality and intensity of odor is not necessarily the sum of its single components, and that single substances are perceived differently than the same substances in a mix. Thus, at the molecular level, odor coding is a function of OSN activity patterns emerging from the combinatorial activation (and inhibition) of subsets of ORs both of which depend on concentration and chemical features of the odor molecules.

Odor Sensing by the Vomeronasal Organ

The VNO expresses a different set of chemosensory receptors, termed vomeronasal receptors (VRs), that also belong to the superfamily of GPCRs but are otherwise distinct from ORs [6]. VRs consist of two unrelated families, V1Rs and V2Rs, that are expressed in the apical and basal layers of the VNO sensory epithelium, respectively. Recent years have shown that vomeronasal sensory neurons detect a number of pheromones (see [7] for historic definition of the term pheromone) that mediate species-specific behavioral repertoires [1]. However, the VNO also detects some general odors without known pheromonal actions.

Compared to ORs, little is known about the chemical features or binding characteristics of VRs. From a chemical perspective, some of the molecules that stimulate the apical, V1R-expressing VSNs represent typical volatiles that for the human nose, would encode a specific odor quality. In some cases, the compounds are not specific for the VNO, but are detected by both mOE and VNO [1]. For example, 2, 5 dimethylpyrazine, a candidate key-food odorant for humans (with a smell of roasted beef), is also present in mouse urine and is known to delay puberty in mice (Fig. 2). The volatile 2-heptanone that has a fruity odor quality, is a male urinary compound that conveys pheromonal action by extending estrus in female mice (Fig. 2). For 2-heptanone two distinct mouse receptors have been identified, the vomeronasal receptor V1R2b and the olfactory receptor OR912–93 both of which are activated at nanomolar concentrations.

The basal, V2R-expressing layer of the VNO appears to be involved in the detection of nonvolatile ligand families, consisting of peptides and proteins, which requires direct physical with the stimulus source. One such family consists of antigenic peptides – the major hitocompatibility complex (MHC) class 1 peptides – that are crucial in the context of immune surveillance and carry information about the genetic make-up of an individual [1]. Interestingly, such MHC peptides are also detected in the mOE, which gives further support to a model involving parallel processing of the same social odor cues by the two olfactory subsystems (Fig. 2). Convergent information derived from the two olfactory systems is likely integrated by higher brain centers.

Odor Processing by Higher Brain Centers

How is odor information represented in the brain? The olfactory glomeruli of the main olfactory bulb (mOB) form the first relay station in the brain where axonal projections of OSNs synapse onto second order neurons, the mitral and tufted cells. It is well-established that odor stimulation evokes spatially and temporally distinct glomerular activation patterns in the mOB that result from the differential activation of specific sets of ORs in the mOE [8] (e.g., see http://leonserver.bio.uci.edu). The brain then needs to extract the features of these bulbar activity patterns. These depend to some extent on chemical odor properties, mainly functional group and structure. For example, molecules with identical functional group, but different C-chain length activate in part overlapping glomeruli that are not activated by structurally related compounds with different functional

groups; single molecules with two different functional groups activate glomeruli that are distinct from those responding to binary mixtures.

Attempts to correlate molecular and functional results on odor coding in rodents with those derived from human psychophysics show that the relation between odor structure and perceived odor quality is still poorly understood. The fact that chemically closely related molecules can confer different odor qualities, whereas molecules that smell alike do not necessarily share chemical similarity suggests that molecular properties and their translation into neuronal activity patterns and spatial odor images in the mOB are not the only determinants in defining odor quality. Further processing of olfactory information by higher brain centers that eventually produce an olfactory percept is only beginning to be understood. Many olfactory-associated brain functions derive from psychophysical studies on humans with discrete brain lesions. Functional imaging of brain activity in humans provides a promising technique to decipher the neural basi of odor perception.

Mitral and tufted cells in the mOB transmit their output signals to the olfactory cortex (Fig. 3), a broadly defined area that consists of the anterior olfactory nucleus, the olfactory tubercle, the piriform cortex, the entorhinal cortex, and the cortical amygdaloid nuclei. The amygdala, which is part of the limbic system and associated with emotional state, participates in formation and storage of olfactory memory.

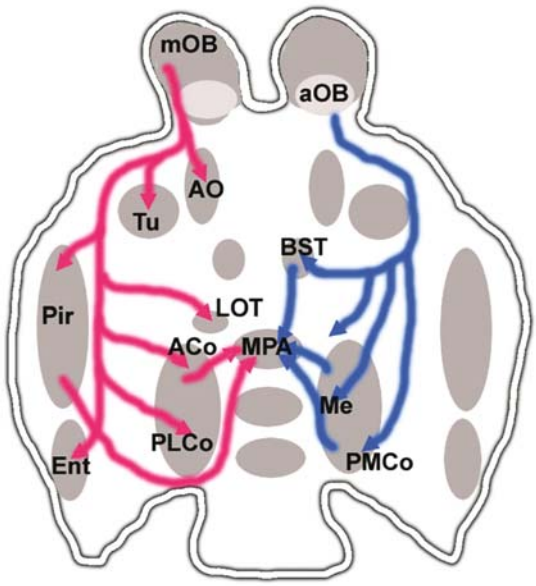
The entorhinal cortex that projects to the hippocampus plays a role in associative learning and olfactory memory. The orbitofrontal cortex receives afferents from parts of the olfactory cortex through the thalamus and is involved in the conscious perception and discrimination of odor. Recent studies connect the piriform cortex with mechanisms in odor identification as well as olfactory memory and learning. Its anterior region, the principal target of mOB output signals, has been suggested to synthetize information about odor structure into a quality percept.

Mitral cells of the aOB project to the medial amygdala, which regulates social behaviors such as mating and recognition of conspecifics. Odor information of the mOB and the aOB is possibly integrated by hypothalamic gonadotropin-releasing hormone (GnRH) neurons resulting in changes in endocrine status and social/sexual behavioral outputs [9]. Furthermore, odor information undergoes additional refinement by higher cortical centers that integrate olfactory input with previous odor experience, afferents from other sensory systems, and in the case of humans, information obtained through language.

Odor Function

Odor cues play an important role in the perception of the environment and in the overall survival of a species. During breathing, air-composition is constantly and involuntarily evaluated. In addition to locating potential food sources, detection (and secretion) of odor has multiple functions in inter- and intraspecies chemical communication, i.e., in the identification of prey, predators, mates, and in the adjustment of social and reproductive behavior. Social behaviors are mediated by both the main and accessory olfactory systems. Common to many mammals is the marking of landscape by depositing individual odors. These complex odor messages carry information about gender, sexual and social status, territoriality, mood, and fitness. In chemical communication, scent marks often serve to deter rivals and attract potential mates. Across many species, scent marks elicited by predators are interpreted as warning signs causing escape behavior. Dogs and wolves produce scent marks through urination and defecation, whereas foxes have developed a specialized supracaudal gland that constantly secretes a mixture of volatile terpenes.

A particularly well-established, odor-induced social behavior is the suckling behavior of rabbit pubs. The milk of female rabbits contains 2-methyl-2-butenal (Fig. 2), a volatile pheromone that guides pups towards their mother's nipples and triggers immediate



Odor. Figure 3 Brain pathways for odor processing emerging from the main olfactory bulb (mOB, red), the accessory olfactory bulb (aOB, blue), and their predicted targets in the mouse brain. *Aco* anterior cortical amygdaloid nucleus; *AO* anterior olfactory nucleus; *BST* bed nucleus of the stria terminalis; *Ent* entorhriunal cortex; *LOT* nucleus of the lateral olfactory tract; *Me* medial amygdala; *MPA* medial preoptic area; *Pir* piriform cortex; *PLCo* posterolateral cortical amygdaloid nucleus; *PMCo* posteromedial cortical amygdaloid nucleus; *Tu* olfactory tubercle.

suckling. Another well-known odor-mediated behavioral change depends on the steroid androstenone (Fig. 2), which induces mating stance in female pigs during heat.

In humans, the smell of androstenone is described as both unpleasant (sweat, urine) or pleasant (floral, sweet). Although present in human axillary sweat and urine, it is not yet clear whether androstenone represents a human pheromone. However, androstadienone (Fig. 2), a related compound in male human sweat, is known to affect endocrine status by maintaining high levels of the hormone cortisol in exposed women. Another example of odor-induced endocrine change in humans derives from odor stimulation of females with armpit or vagina secretions from donor females. Estrus cycles of acceptor females synchronize with that of the donor female ("McClintock" effect) by either advancing or retarding menstruation.

References

1. Brennan PA, Zufall F (2006) Pheromonal communication in vertebrates. Nature 444:308–315
2. Amoore JE (1963) Stereochemical theory of olfaction. Nature 198:271–272
3. Buck L, Axel R (1991) A novel multigene family may encode odorant receptors: a molecular basis for odor recognition. Cell 65:175–187
4. Zhao H, Ivic L, Otaki JM, Hashimoto M, Mikoshiba K, Firestein S (1998) Functional expression of a mammalian odorant receptor. Science 279:237–242
5. Malnic B, Hirono J, Sato T, Buck LB (1999) Combinatorial receptor codes for odors. Cell 96:713–723
6. Dulac C, Axel R (1995) A novel family of genes encoding putative pheromone receptors in mammals. Cell 83(2):195–206
7. Karlson P, Lüscheri M (1959) Pheromones: a new term for a class of biologically active substances. Nature 183:55–56
8. Johnson BA, Leon M (2007) Chemotropic odorant coding in a mammalian olfactory system. J Comp Neurol 503:1–34
9. Boehm U, Zou Z, Buck LB (2005) Feedback loops link odor and pheromone signaling with reproduction. Cell 123(4):683–695

Odor Memory

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Synonyms

Memory-odor; Odor learning; Olfactory learning

Definition

►Odor memory is the store of information about an odor that enables an animal to recognize an odor along with its associations and meaning and link it to an appropriate behavioral response. Olfactory learning is process by which the nervous system forms such odor memories.

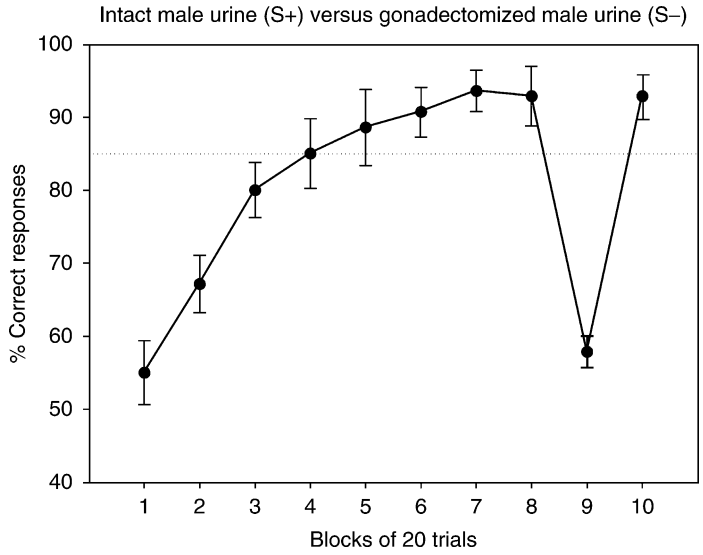
Characteristics

The ability to learn to recognize a particular odor and associate it with a meaning or a predictive value can be demonstrated in a wide variety of vertebrates and invertebrates, and has been studied intensively in terrestrial mollusks, fruit flies, honeybees, rodents and primates. The odor stimuli used in such experiments can consist of individual ►odorants, odorant mixtures or complex, naturally occurring odors containing hundreds of constituents. Olfactometers can be used to carefully control the concentration of odorants and the composition of odor mixtures in the sampled air. Odorant mixtures are generally perceived and learnt as unitary sensory objects, rather than being analyzed in terms of their individual components [1].

One of the simplest form of olfactory learning is a "Go, No-Go" successive odor discrimination, in which an animal is rewarded for making a behavioral response to the rewarded odor (CS+), with no reward delivered in response to the unrewarded odor (CS−). This type of learning is comparatively rapid, occurring within tens of conditioning trails and the memory can last for months (Fig. 1).

Furthermore, the memory for the correct responses to a pair of odors is robust to subsequent learning of other odor pairs, and the learning of subsequent odor pairs is more rapid as the animal learns a win-stay, lose-shift strategy. This results in the ability of rats to learn the correct responses to a new pair of odors after only few trials, which is comparable to the ability of primates to learn visual discriminations. Rodents can also learn to discriminate odors presented simultaneously, either at separate odor ports or in air flowing down separate arms of a Y maze. These discriminations can be made extremely rapidly and it has been estimated that the time to make the discrimination is as small as 220 ms, less than the time taken for a single sniff [2].

Short-term memory (►memory, short-term) for odors can be tested using a delayed non-matching to sample procedure. In this procedure, subjects are presented with a sample odor, which is removed and then, after a variable delay, the subjects are presented with the simultaneous choice of the same odor and a different odor. Responses to the odor that is different from the sample odor are rewarded. Using this task, rats can be shown to have short-term memory for odors of at least 60 s. Moreover, rats can also be trained to learn odor sequences where the correct odor choice depends on the sequence of preceding



Odor Memory. Figure 1 Typical learning curve for a "go, no-go" odor discrimination task for a group of seven inbred mice (Keller and Bakker unpublished data). The learning criterion of 85% correct responses was achieved by the fourth daily block of 20 trials. In block nine the same (S+) stimulus was used for S+ and S− trials. The drop in performance to chance levels demonstrates that the mice were using odor cues to perform the task rather than any extraneous sensory cues associated with the training procedure.

odors, which has been proposed as a test of episodic memory [3].

Rewarding and aversive training stimuli result in learning to approach or avoid the conditioned odor, respectively. However, animals can also learn about the familiarity of odors that have not been paired with any overt training stimulus. If an animal is presented with a novel odor it will initially spend time investigating it. Subsequent presentations of the same odor elicit reduced investigation, as the response habituates, whereas presentation of a novel odor elicits intense investigation. This forms the basis of the ►habituation/dishabituation test of olfactory discrimination, which in some ways is a more natural test of olfactory behavior, but requires the animal to be motivated to investigate the stimulus in the first place. Many innately attractive odors, such as urine odors in the case of rodents, may contain pheromonal components that can act as rewarding stimuli for the associative learning of non-pheromonal odors [4].

In many ways, odor learning has been most extensively studied in humans, who have the advantage of not requiring explicit reinforcement for learning to occur, as they can give verbal responses. However, the very fact that humans can name odors poses problems, in that it is often difficult to dissociate the odor memory from the memory for the verbal label. The association of a verbal label with an odor is a separate process from the recognition of an odor [1]. This is demonstrated by the "tip-of-the-nose" phenomenon in which a person reports that they recognize an odor, and its name is on the tip of the tongue, but they can't quite recall it.

Neural Changes Underlying Odor Learning

A vast number of individual odorants are able to stimulate ►olfactory receptor proteins on olfactory sensory neurons (OSNs). If present at a sufficient concentration then the neural activity that is evoked by an odorant can lead to the perception an odor. However, most odors in nature are not the result of single odorants, but arise from complex mixtures of many odorants. The neural activity evoked by a mixture of odorants that come from a single source are associated to synthesize a unitary neural representation of the odor, known as an odor object. This allows the odor to be discriminated from similar odors and used to recognize and locate the source of the odor. The neural representation of the odor is also associated with neural representations of the object derived from other sensory systems, as well as the context in which it is perceived, and ultimately its meaning for the animal. The ability to subsequently recall these associations in terms of recognizing the odor and its meaning constitute the odor memory. This is not a trivial task. For instance, over 500 individual odorants contribute to the odor of fresh coffee. A few major components will be common between different varieties of coffee. These are the main contributors to coffee odor and will lead to different varieties being classified as coffee. It is the differences

in the numerous minor components that give rise to the fine distinctions between the different coffee varieties, and the ability to make such fine discriminations is enhanced by prior experience with the odors and the importance of making the discrimination [1].

In mammals, the process of associating odorant features into an odor object that can be readily discriminated from similar odors is primarily a function of the ►main olfactory bulb (MOB), anterior olfactory nucleus and anterior piriform cortex, at the initial stages of olfactory processing. OSNs in the main olfactory epithelium express a single odorant receptor type and respond to a small range of odorants with certain shared structural and functional attributes. ►Mitral cells in the MOB receive input from OSNs expressing a single receptor type. However, the responses of mitral cells in the MOB do not simply depend on the input that they get from the sensory neurons. They are also influenced by the arousal and motivational state of the animal, such as whether it is hungry, or the possible presence of a predator. In addition, mitral cell activity is likely to be influenced by a centrally generated expectation of an odor arising from reciprocal connections with higher-level olfactory processes, and activated in situations such as a predator searching for a particular type of prey.

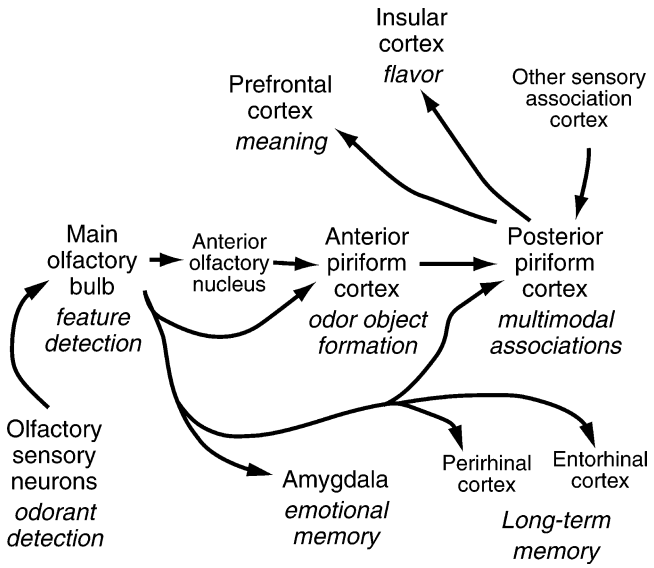
Significantly, there is accumulating evidence that the responses of mitral cells in the MOB depend not only on information provided by OSNs, but also on the meaning of the odor. Hence, the odor-evoked activity of mitral cells in the MOB has been found to change following learning a new reward association for an odor [5]. Such learning-dependent changes in the odor-evoked pattern of neural activity in the MOB are likely to be at least partially the result of changes in gain of lateral and recurrent inhibition from granule cell interneurons. The change in spatiotemporal pattern of mitral cell activity following learning has been hypothesized to "pull apart" the representation of the learned odor from those of similar odors generated by the MOB. This could increase the probability that they could be discriminated reliably and linked to different behavioral responses. There is evidence for this type of decorrelation of odor-evoked patterns of activity in the honeybee antennal lobe (the insect equivalent of the mammalian MOB) following appetitive odor conditioning [6].

Information from individual mitral cells in the MOB is distributed to a large number of pyramidal cells by virtue of their highly divergent projections to the anterior piriform cortex. Conversely, each anterior piriform cortex pyramidal neuron samples information from a large number of mitral cell neurons across a large extent of the MOB. It is thought that these pyramidal cells can therefore act as coincidence detectors. According to this hypothesis, when the pyramidal cells in the anterior piriform cortex receive synchronized input from a sufficient number of mitral cells, the strength of those inputs is enhanced, increasing the probability that the same combination of inputs will cause that pyramidal cell to fire in the future. This is supported by evidence arising from ►cross-adaptation to odorant mixtures. This suggests that whereas mitral cells at the level of the olfactory bulb respond to individual odorants, pyramidal cells in the anterior piriform cortex respond to specific combinations of odorants that form an odor object [1]. Moreover, the pattern of interconnectivity of the anterior olfactory nucleus and anterior piriform cortex is thought to confer pattern completion properties on the network, in which a degraded pattern of input is able to trigger activity in the complete network of pyramidal neurons that respond to the odor object [7]. This might underlie the ability of the olfactory system to cope with the naturally occurring variability in odorant mixtures that are generalized to a particular odor memory.

Higher-Level Brain Areas Involved in Odor Learning

The network of cells in the anterior piriform cortex that represent an odor object communicate with cells in the posterior piriform cortex, which also receive direct input from the olfactory bulb and have widespread reciprocal connections with other brain regions. The interconnections of the posterior piriform cortex suggest that it is likely to function at a similar level to association cortex in other sensory systems and may be involved in forming multimodal representations of stimuli [7]. For instance, the posterior piriform cortex is likely to be involved in associating the sight, sound and smell of a predator into a single representation that can be recalled by input from any one ►modality. Perhaps the most important multimodal representations of odors are in relation to the taste, smell and texture of food, which combine to a representation of flavor, which appear to be stronger than those formed between odors and other sensory modalities. Neurons with multimodal responses to both taste and smell have been found in the orbitofrontal cortex and insular cortex of primates.

Finally these odor representations have to drive an appropriate response. This can be an innate response – especially in the case of ►pheromones. However for the majority of odors, the appropriate response is learned as a result of experience. The amygdala is particularly involved in eliciting learned emotional responses to odors, whereas neurons in the orbitofrontal cortex have been shown to respond to the meaning of an odor and the context in which it occurs. However, it should be remembered that there are extensive reciprocal connections among these areas, and the neural changes that underlie odor memory are distributed throughout all levels of the olfactory system (Fig. 2).



Odor Memory. Figure 2 Major brain areas involved in distinct aspects of odor memory. Extensive reciprocal connections and interconnections between brain areas have been omitted for clarity.

Importance of Odor Learning in Mammals

Odor memory is vital for the recognition of significant elements of the environment, such as food, predators and prey, as well as social cues that enable individual and kin recognition, and odor cues used for navigation. The sense of smell plays a particularly important part in mother-offspring interactions, which are vital for the reproductive success of most mammals. For example, ewes rapidly learn to recognize their own lamb by its odor, within a few hours of giving birth. This odor memory enables the ewe to discriminate between its own lamb, to which it shows acceptance behavior, and alien lambs, which it rejects. Formation of the memory for own lamb odors occurs during a period of a few hours, triggered by the vaginocervical stimulation of birth, and involves dramatic changes in the responsiveness of mitral cells in the MOB to lamb odors [8].

Odor learning is also important for neonatal mammals, especially those that are altricial, in which hearing and sight are poorly developed at birth. For instance, the rabbit mammary pheromone 2-methyl-but-2-enal not only acts as a pheromone to elicit nipple search behavior, but also acts as an unconditioned stimulus to induce memory formation to the maternal odors, or artificial odors that have been applied to the mother [4]. These conditioned odors are then able to elicit full nipple search behavior and therefore reinforce the innate response to the pheromone.

Adult rats can readily be trained to avoid an odor, which has previously been associated an aversive stimulus, such as a mild electric shock. This conditioned fear response is dependent on the amygdala, and is adaptive in helping the rat to avoid potentially dangerous environmental situations. However, if rat pups are exposed to an odor that has been paired with the aversive stimulus of a mild electric shock before postnatal day 10, they will learn to approach the odor [9]. Again this odor memory is adaptive, as at this age the rat pups are normally confined to the nest and are dependent on their mother for their survival. No matter how rough the nest environment or their mother is towards them, the pups remain attracted to the maternal odor. Therefore the function of odor memory can alter to adapt to the changing behavioral priorities of an animal during the course of postnatal and adult life. Moreover, the long-term memory (►memory, long-term) of neonates for odors learned in the nest environment, or even *in utero*, can have lasting effects on their behavior as adults, such as post-weaning food preferences or their choice of mate.

References

1. Wilson DA, Stevenson RJ (2006) Learning to smell. The John Hopkins University Press, Baltimore, MD
2. Uchida N, Mainen ZF (2003) Speed and accuracy of olfactory discrimination in the rat. Nat Neurosci 6:1224–1229
3. Fortin NJ, Agster KL, Eichenbaum HB (2002) Critical role of the hippocampus in memory for sequences of events. Nat Neurosci 5:458–462
4. Coureaud G, Moncomble A-S, Montigny D, Dewas M, Perrier G, Schaal B (2006) A pheromone that rapidly promotes learning in the newborn. Curr Biol 16:1956–1961
5. Kay LM, Laurent G (1999) Odor- and context-dependent modulation of mitral cell activity in behaving rats. Nat Neurosci 2:1003–1009

6. Faber T, Joerges J, Menzel R (1999) Associative learning modifies neural representations of odors in the insect brain. Nat Neurosci 2:74–78
7. Haberly LB (2001) Parallel-distributed processing in olfactory cortex: new insights from morphological and physiological analysis of neuronal circuitry. Chem Senses 26:551–576
8. Brennan PA, Kendrick KM (2006) Mammalian social odors: attraction and individual recognition. Philos Trans R Soc Lond B Biol Sci 361:2061–2078
9. Sullivan RM, Landers M, Yeaman B, Wilson DA Good memories of bad events in infancy. Nature 407:38–39

Odor-binding Proteins

►Odorant-Binding Proteins

Odor Cells in Hippocampus

Definition

In a series of studies aimed at exploring the role of hippocampal function in memory using the model system of olfactory-hippocampal pathways and odor learning in rats, it has been demonstrated that hippocampus itself is not essential to memory for single odors, but is critical for forming the representations of relations among odor memories, and for the expression of odor memory representations in novel situations. The studies that exploit the exceptional qualities of olfactory learning are helping to clarify the nature of higher order memory processes in all mammals, and extending to declarative memory in humans.

►Olfaction
►The Hippocampus: Organization

Odor Code

►Odor Coding
►Olfactory Information

Odor Coding

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Synonyms

Odor code; Olfactory code; Olfactory coding; Odor representation

Definition

The processes by which essential features of odor molecules are translated into patterns of neural activity in the olfactory circuit.

Characteristics

A code is a set of rules allowing the translation of information from one form or dimension into a different one, in such a way that essential features of the original message are preserved and made available for further unambiguous reading and information extraction. In the case of odors, the nervous system translates the information pertaining to chemical stimuli into patterns of neural activity at the first stages of processing in the brain. We focus here on odor encoding within the vertebrate olfactory bulb (OB) and the analogous circuit in insects, the antennal lobe (AL), excluding specialized pheromonal centers and higher-order centers of the olfactory circuit.

Odor molecule determinants such as chain length (number of carbon atoms), functional group (aldehyde, alcohol, ketone, etc.) and concentration, among others, seem to be the sensory primitives that are processed by the olfactory pathways. They are transduced from the chemical world into the neural domain by differential activation of olfactory receptor proteins on the surface of olfactory sensory neurons, on the insect antenna or in the nose of vertebrates.

The olfactory message is first processed at the level of the primary olfactory centers in the brain (the AL in the case of insects and the OB in the case of vertebrates). Both the AL and the OB are organized according to similar anatomical principles. They are constituted by glomeruli, which are the anatomical and functional units involved in the first steps of odor processing in the nervous system. Olfactory receptor neurons expressing the same receptor type converge to one or a few glomeruli [1] so that the response of a glomerulus is an amplified version of the responses of the receptor type under consideration. There are up to several hundred glomeruli in an insect antennal lobe and several thousand in a vertebrate olfactory bulb. Glomeruli are not simple convergence sites of olfactory receptor axons; they are interconnected by different sets of local

inhibitory neurons, which release the inhibitory neurotransmitter GABA (γ-aminobutyric acid), thus producing complex patterns of firing activity in response to an odor. In insects, local inhibitory and excitatory interneurons may connect laterally few or multiple glomeruli. In vertebrates, lateral inhibitory connections are provided by periglomerular cells whose dendrites are restricted to one glomerulus and by short axon cells which have dendrites and axons extending throughout several glomeruli. In addition, a second level of powerful inhibitory connections is provided by the interaction between granular cells and output cells to the OB.

The processed signal is further conveyed to higher-order centers by such output neurons, the projection neurons in insects and the mitral/tufted cells in vertebrates. Thus, once odors activate groups of receptor neurons, the information does not simply flow through the AL/OB to downstream areas via projection neurons or mitral cells. Instead, the presence of inhibitory neurons within the neural network of the AL/OB determines a global reformatting of odor representations, in the form of a stimulus-dependent, spatio-temporal redistribution of activity across the AL/OB [2].

The olfactory code is a spatio-temporal code in that it contains two complementary components, the spatial and the temporal dimensions. Each of these two dimensions has been studied using different techniques, mainly imaging for the spatial code, and electrophysiology for the temporal code. The impression that such different analyses correspond to separate, unconnected properties of the olfactory code should be avoided. Spatial and temporal properties of the olfactory code represent, in fact, different sides of the same coin.

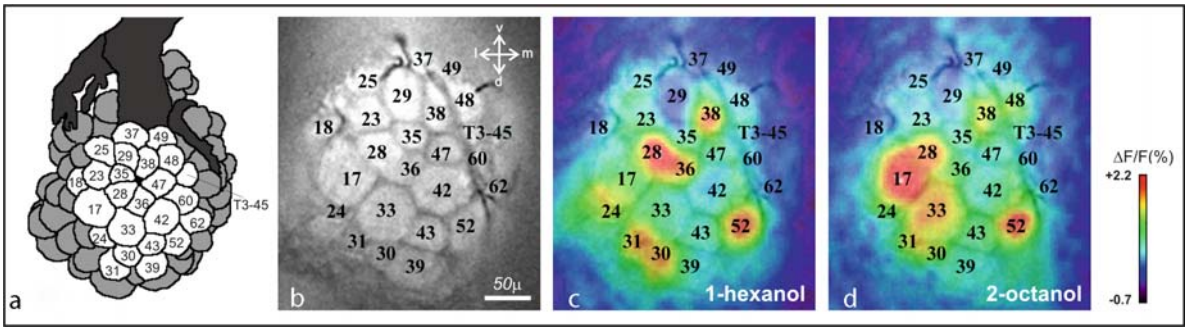
Spatial Coding of Odors

Odors may be encoded at the level of the AL/OB in terms of a specific spatial pattern of glomerular activation (Fig. 1).

Such activity pattern constitutes an odor map, which is proper to each odor, symmetric between hemispheres and conserved between individuals [3]. Spatially distributed activity patterns relate to certain structural features of the odor molecules as molecules with similar structural properties are encoded in terms of partially overlapping activity patterns. Neural similarity, measured in terms of the amount of overlap of glomerular activation patterns, correlates directly with perceptual similarity, measured in terms of behavioral odor choices [4], i.e. odors judged as similar correspond to partially coincident odor maps.

Odor concentration affects the odor map as generally, the number of activated glomeruli increases with increasing concentrations of the stimulating odor. A critical question would be, therefore, how ►concentration invariance is achieved given the changing nature of this odor representation. A possible answer comes from the fact that, as mentioned above, spatial coding is not the unique form of translating chemical stimulus features into patterns of neural activity (see below "Temporal coding").

Quantifying glomerular activity requires identifying individual glomeruli across preparations in the same or different individuals. To this end, atlases of the primary olfactory center have been established in the case of the antennal lobe of some insects (honeybees, moths, flies) where such an approach is accessible due to a lower number of constitutive glomeruli.



Odor Coding. Figure 1 Spatial coding of odors at the level of the antennal lobe of the honeybee *Apis mellifera*. (a) Atlas of the honeybee antennal lobe showing 24 glomeruli individually identified. (b) Example of an anatomical staining of the frontal part of a left antennal lobe with the 24 identified glomeruli (*d* dorsal; *l* lateral; *m* medial; *v* ventral). (c) Calcium-imaging recordings of neural activity *in vivo* upon odor stimulation of a honeybee. Superimposed activity map in response to the odor 1-hexanol, showing which glomeruli were activated. The colors (see scale on the right) represent activity levels in terms of fluorescence variation (ΔF/F %) with respect to a basal level (no olfactory stimulation). (d) Superimposed activity map in response to the odor 2-octanol. Each odorant is encoded by a specific spatial pattern of glomerular activation.

Olfactory maps can be visualized using different kinds of techniques allowing measurements of neural activity upon olfactory stimulation. Markers of neural activity vary from radiolabels ([^{14}C] 2-deoxyglucose) and antibodies (*c-fos*) to fluorescent dyes (voltage-sensitive or calcium reporters), or intrinsic optical properties of the tissue. Using some of these and other techniques it is possible to disentangle the contributions of olfactory receptors conveying the olfactory message to the brain from that of local interneurons and projection neurons conveying such a message to higher-order brain centers. In this way, the role of the different neural subpopulations in the elaboration of the odor map can be understood. Assessing the respective contributions of pre- and postsynaptic elements is crucial for understanding the computations carried out at the level of the AL/OB.

Activity maps in the AL/OB are not static but dynamic odor representations. Such a dynamics mostly reflects interglomerular interactions within the AL/OB. However, at the level of sensory afferences to the glomeruli of the OB, diverse, glomerulus- and odorant-dependent temporal dynamics are already present, thus showing that glomerular maps of primary sensory input to the OB are temporally dynamic, even before further processing within the bulb. These dynamics may contribute to the representation of odorant information and affect information processing in the central olfactory system.

Temporal Coding of Odors

Comprehensive studies on the temporal coding of odors have been performed in several species but studies on locusts have been crucial to understand the principles governing this coding [2]. Such studies have shown that both monomolecular and complex odors are encoded combinatorially by dynamical assemblies of projection neurons. Information about odor identity is contained in the timing of action potentials in an oscillatory population response, rather than on the mere spiking frequency of the response.

Indeed, each projection neuron in an odor coding assembly responds with an odor-specific temporal firing pattern consisting of periods of activity and silence. Any two projection neurons responding to the same odor are usually co-active only during a fraction of the population response. The spikes of coactivated projection neurons are generally synchronized by the distributed action of local interneurons in the AL, which release GABA. Because projection neurons convey the olfactory information to higher-order structures, the mushroom bodies, the coherence of projection neuron activity can be measured in this target area in terms of local field potential (LFP) oscillations [2]. LFP oscillations have a frequency of 20–35 Hz. Each successive cycle of the odor-evoked oscillatory LFP can therefore be characterized by a co-active subset of projection neurons. As a consequence, each odor is encoded by a specific succession of synchronized assemblies [2]. The action potentials produced by a projection neuron during its odor-specific phases of activity are not necessarily all phase-locked to the LFP. For each odor–projection neuron combination, however, precise and consistent epochs of phase-locked or non-phase-locked activity can be identified (Fig. 2).

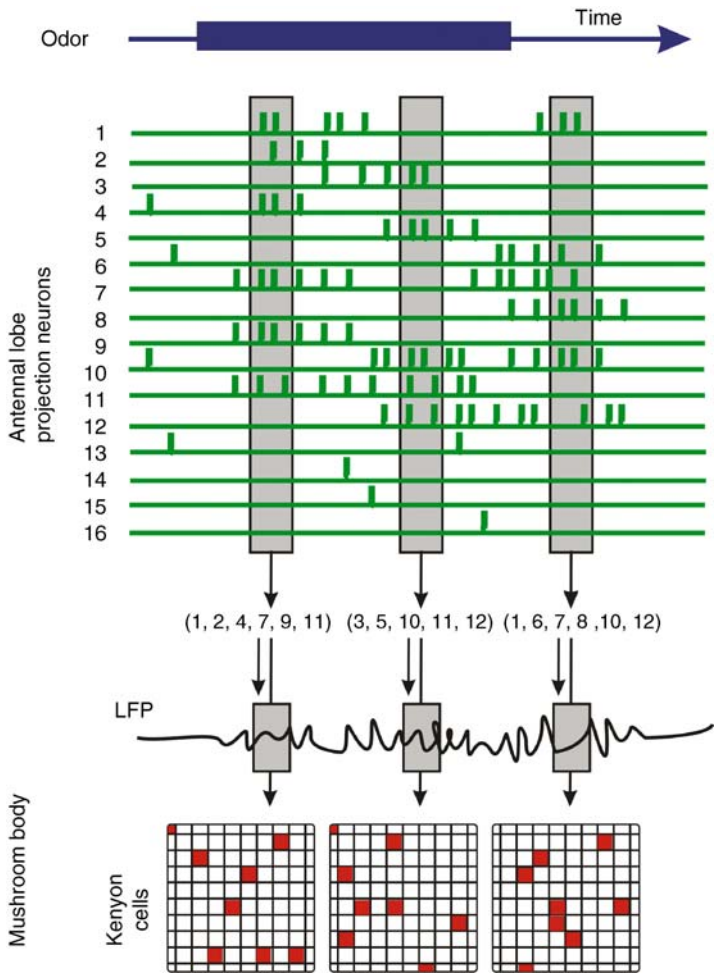
Increased odor concentration leads to changes in the firing patterns of projection neurons, similar to those caused by changes in odor identity, potentially confounding representations for identity and concentration. However, concentration-specific response patterns cluster by identity, resolving the apparent confound. Thus, odor encoding comprises three main aspects: the identity of the odor-activated neurons, the temporal evolution of the ensemble, and oscillatory synchronization.

Besides oscillatory synchronization, the odor-evoked responses of local interneurons and projection neurons also contain prolonged and successive periods of increased and decreased activity (slow response patterns), which are cell and odor specific and are stable from trial to trial. Hence, oscillatory synchronization and slow patterning together shape a complex, distributed representation in which odor-specific information appears both in the identity and in the time of recruitment and phase-locking of projection neurons.

Experiments on honeybees [5] showed that oscillatory synchronization between projection neurons is selectively abolished by picrotoxin, an antagonist of the $GABA_A$ receptor acting on GABA-ergic local interneurons of the antennal lobe, and that such a picrotoxin-induced desynchronization impairs the behavioral discrimination of molecularly similar odorants, but not that of dissimilar odorants. It was, therefore, suggested that oscillatory synchronization of neuronal assemblies is functionally relevant, and essential for fine, but not coarse olfactory discrimination. Interestingly, picrotoxin has no effect on the slow response patterns of projection neurons [2], thus showing that other sources of neural inhibition are at play at the level of the AL.

In vertebrates, three types of oscillatory rhythms have been distinguished in the activity of mitral cells, the pendant of insect projection neurons. Based on their frequency spectrum, one can distinguish three oscillation types:

1. θ oscillations (1–8 Hz) are generated by the respiratory rhythm and are correlated with increased and decreased stimulation of olfactory afferences upon inspiration and expiration, respectively. Different mitral cells may exhibit different response latencies to the same odorant and odor coding



Odor Coding. Figure 2 Temporal coding of odors in the locust olfactory system.The presumed odor representation is combinatorial, spatially distributed and relies on synchronized and evolving neural assemblies. An odor stimulus elicits spiking activity in several projection neurons (1–16), which constitute the output to the antennal lobe. For each odor–projection neuron combination, however, precise and consistent epochs of phase-locked or non-phase-locked activity can be identified. The coherence of projection neuron activity can be measured at the level of the mushroom bodies in terms of local field potential (LFP) oscillations. Only few Kenyon cells, the constitutive cells of the mushroom bodies, are activated by projection neuron input (sparse coding) (adapted from Laurent G, Trends in Neurosci 19:489–496, 1996).

models have been proposed based on the phase relationship between action potentials of mitral cells and the phase of a θ cycle [6].

2. β oscillations (15–30 Hz) are induced by the inhalation of odor molecules and their origin is a matter of debate. While some theories posit that β oscillations originate not in the OB itself but in downstream structures (e.g., olfactory cortex) that feedback on it, other theories postulate that rhythmic input on granular cells induce these oscillations. The function of β oscillations is still unclear but it has been shown that olfactory learning and habituation can enhance the prevalence of β rhythm over γ rhythm in an odor-specific manner [7].
3. γ oscillations (40–80 Hz) are present in the olfactory system of several vertebrate species and can be related to those evinced in the olfactory system of insects (see above). These oscillations are generated in the olfactory bulb upon inhalation of odor molecules. Mitral cell activity is synchronized with γ oscillations and such synchronization arises from the interaction between mitral and granular cells. Glutamate released from mitral cell dendrites excites the dendrites of granule cells, which in turn mediate GABA-ergic inhibition back onto mitral cells [8]. Granular cells do not synchronize with γ oscillations; it has been proposed that they release GABA in a rhythmic manner and in absence of action

potentials [8]. Such a rhythmic inhibitory activity seems to play a fundamental role in the modulation of the oscillatory frequency.

Importantly, not all mitral cells are synchronized with γ oscillations during the response to an olfactory stimulus. In fact, the two neural populations, those exhibiting and those not exhibiting synchrony, encode different properties of the odor: non-synchronized action potentials allow encoding the fine identity of an odor while synchronized action potentials encode the category (ensemble of similar odor molecules) to which the perceived odor belongs [9]. Thus, different properties of an odor can be encoded by the same mitral cells depending on their synchronization with the neural population. The role of γ oscillations in olfactory perception in rodents has been demonstrated by experiments on transgenic mice presenting alterations of inhibitory activity in the OB. Such alterations result in significant changes in olfactory discrimination.

The picture emerging from studies on the temporal coding of odors in the AL/OB suggests that the transfer of odor-evoked signals from receptors to the AL/OB circuits is accompanied by a reshaping of odor representations so that stimulus-dependent, temporal redistribution of activity arises across these circuits. Such a reshaping exploits time as a coding dimension and results from the internal connectivity of the AL/OB circuits and from the global dynamics that these connections produce. Moreover, centrifugal connections from higher order centers (e.g. the mushroom bodies in insects, the olfactory cortex in vertebrates) to the AL/OB may also play an important role in reshaping of odor representations. This top-down process is specifically involved during learning condition in which neutral odorants are transformed into ►aversive or ►attractive ones.

Conclusions

All in all, the antennal lobe of insects and the olfactory bulb of vertebrates act similarly upon olfactory stimulation: to prevent ►adaptation, they format and reshape odor representations, increase the signal-to-noise ratio and improve odor discrimination. It appears that spatial and temporal dimensions are complementary aspects of odor coding in the AL/OB circuits and that their separated analysis responds to the use of different recording techniques that have put the emphasis on one aspect or the other. As we have detailed above, temporal variations of the spatial code are observed in imaging experiments, and in the temporal code, odor-specific information appears also in the identity of the active projection neurons, i.e. a spatial-related property. For instance, synchronization of output neuron activity at specific sites within the odor map is crucial as shown by studies in the moth where odors elicit high synchrony of action potentials in paired cells connected to the same glomerulus but low synchrony in cells connected to different glomeruli [10]. Such studies revealed a strong relationship between recording positions, temporal correlations, and similarity of odor response profiles, thus supporting the notion that the olfactory system uses both spatial and temporal coordination of firing to encode chemosensory signals [10]. As shown by this example, future neurophysiological studies should bring the spatial and the temporal dimensions of the odor code together, using recording methods that allow both good spatial and temporal resolution. In this way, characterizing the fine relationship between the temporal and the spatial dimension of olfactory coding at the level of the AL/OB will be possible.

References

1. Mombaerts P, Wang F, Dulac C, Chao SK, Nemes A, Mendelsohn M, Edmondson J, Axel R (1996) Visualizing an olfactory sensory map. Cell 87:675–686
2. Laurent G, Stopfer M, Friedrich RW, Rabinovich MI, Volkovskii A, Arbanel H (2001) Odor encoding as an active, dynamical process: experiments, computation, and theory. Annu Rev Neurosci 24:263–297
3. Kauer JS, White J (2001) Imaging and coding in the olfactory system. Annu Rev Neurosci 24:963–979
4. Guerrieri F, Schubert M, Sandoz JC, Giurfa M (2005) Perceptual and neural olfactory similarity in honeybees. PLoS Biol 3(4):e60
5. Stopfer M, Bhagavan S, Smith BH, Laurent G (1997) Impaired odour discrimination on desynchronization of odour-encoding neural assemblies. Nature 390:70–74
6. Schaefer AT, Margrie TW (2007) Spatiotemporal representations in the olfactory system. Trends Neurosci 30:92–100
7. Martin C, Gervais R, Chabaud P, Messaoudi B, Ravel N (2004) Learning-induced modulation of oscillatory activities in the mammalian olfactory system: the role of the centrifugal fibres. J Physiol Paris 98:467–478
8. Lagier S, Carleton A, Lledo PM (2004) Interplay between local GABAergic interneurons and relay neurons generates gamma oscillations in the rat olfactory bulb. J Neurosci 24:4382–4392
9. Friedrich R, Laurent G (2001) Dynamic optimization of odor representation by slow temporal patterning of mitral cell activity. Science 291:889–894
10. Lei H, Christensen TA, Hildebrand JG (2004) Spatial and temporal organization of ensemble representations for different odor classes in the moth antennal lobe. J Neurosci 24:11108–11119

Odor Detection

Definition

The sensory process by which an external odorant stimulus elicits an odor sensation, without necessarily

identifying the exact quality of the detected stimulus. Odor detection is released when a stimulus reaches the detection threshold (or absolute threshold), that is the lowest stimulus capable of producing a sensation that something has changed in reference to a control stimulus. Odor detection can be conscious or unconscious. Conscious odor detection is ordinarily revealed by behavioral or verbal responses. Unconscious odor detections can be revealed by recording the alteration in the reactivity of the autonomous nervous system. Odor detection is compromised in many conditions, especially in Parkinson disease and the later stages of Alzheimer's disease and following damage to the olfactory mucosa or bulb.

►Alzheimer's Disease
►Olfactory Hallucinations
►Parkinson Disease
►Smell Disorders

Odor Discrimination

Definition

This is the ability to detect differences between odors. This is measured in several ways, all of which involve presenting two different smells and having the participant judge whether they are the same or different. Odor discrimination allows to extract an olfactory signal from a background and to make a distinction between different odorant molecules. Whilst compromised odor detection will always affect identification and discrimination, impaired discrimination (or identification) can occur independently of detection.

►Odor
►Olfactory Hallucinations

Odor Expertise

►Olfactory Perceptual Learning

Odor-exposure Learning

►Olfactory Plasticity

Odor Familiarity

►Olfactory Perceptual Learning

Odor Identification

Definition

This is the ability to correctly provide a name for an odor, when no other cue to its identity is present. This may be measured by simply asking a person to generate a name, or by providing a list of names from which the person has to choose. The most well established test of olfactory functioning, the Smell Identification Test (SIT), utilizes the latter method.

►Odor
►Olfactory Hallucinations

Odor Image

►Odor Maps

Odor Learning

►Odor – Memory

Odor Maps

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Synonyms

Odor image

Definition

Extraction of information from an odor stimulus is a multi-level task for the brain, involving levels of neuronal processing from the odorant receptors up to the olfactory cortex. Sensory modality at each level is represented by activity patterns in two-dimensional neural space. Various sensory signals activate topographically distinct subsets of neurons. Such patterns represent odor ►maps.

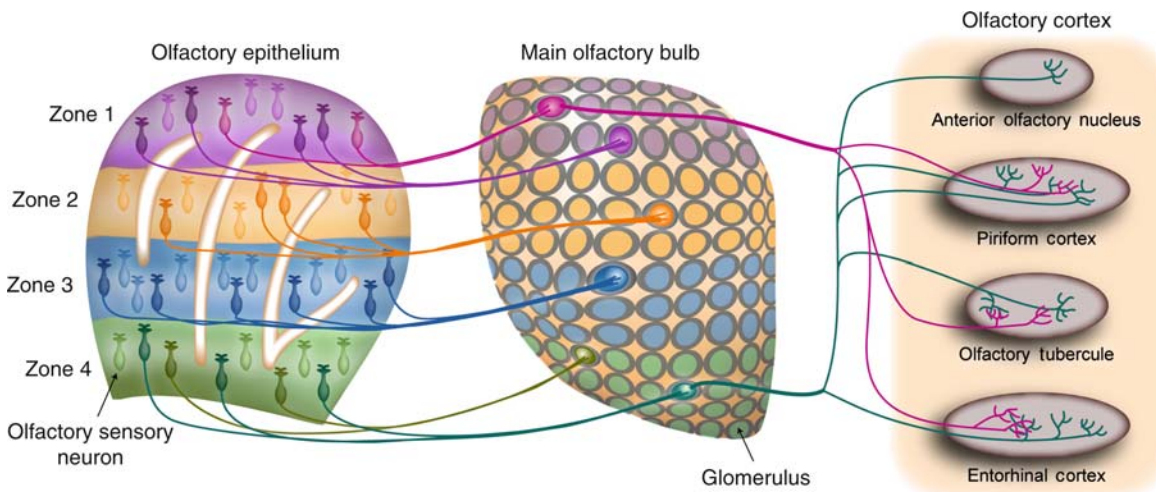
Characteristics

Olfactory Epithelium

Information processing begins with the mapping of an odorant to the subset of receptors that it activates. More than 400,000 compounds are thought to be odorous to the human nose; mammals have developed nearly 1,000 types of odorant receptors to cope with this huge variety of odorants. Odorant receptors are expressed on the cilia of olfactory sensory neurons situated in the nasal olfactory epithelium. Each receptor presumably detects particular ►molecular features of odorants and thus binds to a specific range of odorants sharing common features [1]. However, each odorant can bind to multiple, but specific, odorant receptors. Thus, an odorant or a mixture of odorants will activate a specific combination of odorant receptors located within the olfactory epithelium. At this level, the odor ►map may be considered a map of receptor space, providing practically unlimited coding capacity for the olfactory system. Olfactory sensory neurons usually produce only one odorant receptor type, so the odor map of receptor space directly translates to a map of activated olfactory sensory neurons. A spatial dimension is also present, at least in mammals in which olfactory epithelium is divided into four zones [1]. A given odorant receptor is only produced by sensory neurons distributed throughout one of the four zones (Fig. 1). Domains of receptor production have also been identified in fish and insects.

Olfactory Bulb

In rodents, with few exceptions, olfactory sensory neurons producing the same odorant receptor converge onto two topographically fixed glomeruli, one in the lateral and the other in the medial part of the main olfactory bulb, arising from sensory neurons in the lateral and medial epithelium, respectively. In mice, there are approximately 2,000 glomeruli and their localization is roughly conserved among individuals. Each glomerulus represents a single odorant receptor; thus, the glomerular sheet of the olfactory bulb forms a map of odorant receptors [1]. Furthermore, neurons that are segregated in the epithelium extend to distinct regions of the bulb, such that the spatial topography of the nasal epithelium is preserved in the glomerular sheet, following the principle of a "zone-to-domain" projection (Fig. 1). Thus, two symmetrical sensory maps are generated; one is in the rostrolateral hemisphere and the other is in the caudomedial hemisphere. However, a zone-specific expression pattern in the olfactory epithelium is not present in a small group of odorant receptors. An individual odorant receptor of



Odor Maps. Figure 1 *From odorant receptors to the olfactory cortex:* Olfactory sensory neurons expressing a given odorant receptor are distributed widely in one of the four zones and converge their axons onto a few topographically fixed glomeruli in the olfactory bulb. Each glomerulus represents a single odorant receptor. Mitral cells from the glomeruli form synapses with clusters of neurons in multiple olfactory cortical areas. Inputs from different odorant receptors overlap spatially. (*Olfactory bulb outputs from two glomeruli only are displayed for more clarity*).

this group is typically represented by a single glomerulus located at the most ventral portion of the bulb [2]. Thus, the non-zonal odorant receptors generate a small map at the most ventral part of each main olfactory bulb. Convergence is less strict in the accessory olfactory system (which processes some pheromones) and similar olfactory sensory neurons can converge onto multiple neighboring glomeruli. Nevertheless, odorant quality is represented through spatial patterns of glomerular activation in both cases, reflecting differential activation of olfactory sensory neurons (Fig. 1). This principle of odor mapping is widely observed in various vertebrate species and in invertebrates, including honeybees, moths and flies. Moreover, the odorant-specific spatial positions of activated glomeruli are conserved in animals of the same species.

Individual glomeruli in the olfactory bulb function as molecular-feature detecting units: they respond to a range of odorants sharing specific combinations of molecular features. Furthermore, glomeruli with similar response properties are located in close proximity and form molecular-feature clusters [1]. This is consistent with evidence that sensory neurons expressing homologous odorant receptor genes project their axons to neighboring glomeruli. A precise chemotopic organization is sometimes present within glomerular clusters. For instance, a chemotopic progression with increasing odorant carbon number has been detected in multiple response clusters [2]. So, the glomerular sheet of the bulb topographically represents the characteristic molecular features in a systematic, gradual and multidimensional fashion.

Olfactory Cortex

Each glomerulus is a spherical neuropil containing the axons of several thousand olfactory sensory neurons that establish synapses with dendrites of approximately 50 mitral and tufted cells (the olfactory bulb projection neurons) and local interneurons. Axons of mitral cells carrying input from a given olfactory receptor synapse with multiple specific clusters of pyramidal neurons in the olfactory cortex, generating a stereotyped map of olfactory receptor inputs that is different from that in the olfactory bulb. The projections to the olfactory cortex are diffuse and have characteristics of a combinatorial array, with extensive overlap of afferent inputs and widespread intracortical association connections. Thus, inputs from different odorant receptors are mapped onto partially overlapping clusters of pyramidal neurons [3] (Fig. 1). It appears that individual neurons receive signals from various odorant receptors. Thus, although inputs from various odorant receptors are segregated in the olfactory epithelium and olfactory bulb, single neurons in the olfactory cortex seem to combine multiple inputs. The olfactory cortex is thought to be important for integrating signals from various molecular-feature-detecting units of the bulb.

Mapping Methods

Several mapping methods have been used to identify odor-specific spatial activation patterns in the olfactory bulb in mammals [1]. These methods can be classified into two complementary groups, each with their advantages and disadvantages. The first group has the advantage that the responses are mapped over the entire bulb and includes methods involving functional MRI (fMRI) and assessment of 2-deoxyglucose uptake, expression of immediate early genes (e.g. *c-fos, c-jun, Arc* and *zif268*) and production of phosphorylated ERK. These methods allow investigation of how individual odorants are represented within the entire glomerular sheet of the bulb. The disadvantage of this group is that, with the exception of fMRI, these methods map the response to only one odorant in each animal.

On the contrary, the second group of methods facilitate mapping of the responses to many odorants in the same bulb of an animal. This group includes optical imaging of intrinsic signals, imaging with calcium-sensitive or voltage-sensitive dyes, imaging using pHluorin, electrophysiological recording of single neuron activity and fMRI. With these methods, it is possible to determine the range of odorants that activate an individual glomerulus. However, again except for the fMRI method, these methods allow us to map only the exposed surface of the bulb. Only the dorsal and posterolateral surfaces have been successfully mapped thus far.

Functional Relevance of the Spatial Arrangement of Glomeruli in the Olfactory Bulb

If the spatial map is important to olfactory behavior, then disrupting the map should impair one or more olfactory functions. Slotnick and colleagues tested this hypothesis in a series of behavioral experiments and showed that ablations of large portions of the olfactory bulb and other destruction of olfactory inputs did not significantly impair odor discrimination and detection. Furthermore, animals trained before such manipulations can often still recognize the same odors after ablation. Even rats with no bulb can carry out olfactory discriminations, supported by olfactory nerve inputs that reinnervate areas of the olfactory cortex [4]. Rather than concluding that spatial maps have only a minor function in the olfactory bulb, it may be argued that discrimination and detection of odors are not the computations facilitated by these mechanisms.

Moreover, the chemotopic arrangement of glomeruli in the bulb seems to have a functional relevance. Even though the relationship between the molecular structures of odorants and their subjectively perceived odors is not entirely clear, odorants with similar combinations of molecular features tend to have similar odor qualities, at least for the human nose. Thus, it is possible that molecular-feature clusters of glomeruli are

part of the representation of basic odor quality [1]. There are various lines of evidence that favor this hypothesis. Measurements of spontaneous responses show that rats generalize between odor pairs with very similar glomerular activity maps, but not between odor pairs with different glomerular maps. However, rodents can be trained by differential reinforcement to discriminate between all odor pairs tested to date with high accuracy. Nevertheless, although discrimination performance in rats is always very good, there is still a significant correlation between glomerular map dissimilarity and discrimination accuracy. Lateral inhibition among neighboring glomeruli may allow mitral cells to respond to a narrower range of stimuli than their associated sensory neurons. This possibly permits a smaller overlap in the number of highly activated mitral cells responding to two similar odorants, thus facilitating their discrimination. Lateral projections of interneurons that are distributed more densely between neighboring than distant glomeruli confirm this hypothesis. Therefore, the spatial clustering of glomerular responses may coordinate the principle responses of bulbar projection neurons by way of center-surround functionality implicating inhibitory interneuronal networks.

Despite the accepted correlation between odor maps and odorant structural commonalities, this relationship breaks down if odorant concentration is included as a variable. If odorant concentrations are increased, more glomeruli respond and odor maps broaden and intensify [5]. The recruited glomeruli are located near the originally activated glomeruli due to chemotopic clustering of glomeruli with similar odorant specificities. Higher odorant concentrations recruit additional sensory neuron populations with progressively lower affinities for the presented agonist. However, the qualitative perception of odors is usually not affected by variability in concentration, suggesting that various neural normalization mechanisms can preserve concentration-independent odor quality information. Regardless of concentration, relative levels of glomeruli activation in the bulb are stable and the representation of odor quality may rely on these activity patterns [5]. The impact of stimulus concentration is not as high in mitral cells and increasing odorant concentrations do not monotonically increase their spiking rates. The mechanisms for normalization of olfactory representations are not precisely known, but it is possible that they do not rely on center-surround inhibition, as global normalization has to be carried out for the entire bulb.

Development of the Glomerular Map in the Olfactory Bulb

Creation of the map begins prenatally when axons of olfactory sensory neurons navigate toward the bulb, resort in a receptor-specific manner and terminate in a broad area of the bulb surface, interdigitated with other axon populations. Only postnatally, the axons segregate into completely separate glomerular structures. This maturation process requires various amounts of time, ranging from a few days to about one month, depending on the glomerulus [6]. Very precise axonal targeting is achieved, even for populations expressing highly related odorant receptors and innervating neighboring glomeruli.

The complex processes of axon navigation, fiber sorting and cell recognition are governed by a hierarchical system of recognition and adhesion molecules. Attractive or repulsive interactions apparently drive the growing axons towards or away from regions of the bulb. However, the diversity of the guidance molecules that have been identified is not sufficient to explain the precise topographical glomerular map observed in the bulb. The odorant receptor protein is itself involved in axon guidance and may control the production of guidance molecules and adhesion molecules [7]. Whereas the initial (prenatal) process of glomerulization mainly requires molecular determinants, postnatal activity-dependent processes refine glomerular organization. Whether genetic or activity-dependent mechanisms are dominant in this process of map formation, it is clear that the cues organizing these connections must be present throughout the life of the animal and not only during the initial phases of olfactory development. The olfactory epithelium is continuously self-renewed and olfactory sensory neurons are continuously replaced by newborn neurons that can re-establish good glomerular connections. Thus, the glomerular map does not change throughout adulthood.

Dynamics of the Odor Maps in the Olfactory Bulb

Odorant responses are often considered static spatial entities. However, various factors may influence the primary sensory input to the olfactory bulb and give rise to differences in the timing of glomerular responses to odorants. First, the nature of the airflow in the naris of rodents causes stimuli to arrive at receptors in various expression zones within the olfactory epithelium at different times [2]. There is a chromatographic effect in the nasal cavity and various odorants are chemically converted in the nasal mucosa before linking to their receptors. This may explain how various odorants can activate the same glomeruli with different kinetics. Furthermore, individual sensory neurons expressing the same odorant receptor may have identical odorant response profiles, but different activation thresholds and their axon terminals may be modulated presynaptically. This widens the range of population terminals converging into a single glomerulus. The dynamics of glomerular activation also depends on the breathing cycle and changes within a respiration cycle and from one cycle to the next [8]. Thus, whereas some glomeruli respond less strongly during the second breathing cycle, suggesting that adaptation occurs, others respond more

strongly, indicating that other processes also contribute to the dynamics observed. The active inhalation pattern of the animals also controls adaptive filtering to detect changes in odor landscape. Thus, neural representations of the same odorant sampled during low-frequency passive respiration and high-frequency sniffing differ [9]. Consequently, glomerular odorant responses differ in amplitude, latency and rise time in an odorant-specific manner and is also dependent on sniffing behavior for a particular odorant. Conjointly, mitral and tufted cell activities also demonstrate stimulus-specific temporal structure. Thus, a temporal code for odorant quality may be embedded in these temporal bulbar activation differences. Spatial distribution and the temporal structure of neuronal activity should therefore not be studied in isolation, but considered as a single entity of the same coding process. Currently, although there is increasing evidence for the importance of temporal structure in bulb odorant-evoked output, little is known about how this temporal patterning is translated within cortical neural ensembles.

Most studies on odor maps have been done with naive animals and have confirmed that they are conserved from one individual to another within the same species. Depending on the mapping method, these maps are not entirely similar because they require animals that are either awake or anesthetized. Anesthesia may itself modify odor processing. In animals that are awake, the output of the olfactory bulb represents the integration of odor stimuli and behavioral variables relevant to odor expectation, discrimination, context and predictive associations. Thus, a certain degree of map flexibility is expected, depending on the behavioral context and on the physiological state of the animal. The fact that the spatio-temporal output of the bulb is affected by learning is consistent with this theory. Training can modify the odor map [10], challenging the findings of studies that put in parallel behavioral performances of trained animals and odor maps of naive animals. Odor maps are dynamic and various changes, particularly those induced by training, may be long-lasting. The centrifugal fibers that richly innervate the bulb can modulate odorant perception and may affect spatial and temporal patterning of glomerular activation. Another factor of bulbar functional plasticity is the continuous neurogenesis occurring in the bulb. Learning induces changes in neurogenesis in the bulb, which may support long-lasting changes in odor maps.

References

1. Mori K, Takahashi YK, Igarashi KM, Yamaguchi M (2006) Maps of odorant molecular features in the Mammalian olfactory bulb. Physiol Rev 86:409–433
2. Johnson BA, Leon M (2007) Chemotopic odorant coding in a mammalian olfactory system. J Comp Neurol 503:1–34
3. Zou Z, Li F, Buck LB (2005) Odor maps in the olfactory cortex. Proc Natl Acad Sci USA 102:7724–7729
4. Slotnick B, Cockerham R, Pickett E (2004) Olfaction in olfactory bulbectomized rats. J Neurosci 24:9195–9200
5. Cleland TA, Johnson BA, Leon M, Linster C (2007) Relational representation in the olfactory system. Proc Natl Acad Sci USA 104:1953–1958
6. Strotmann J, Breer H (2006) Formation of glomerular maps in the olfactory system. Semin Cell Dev Biol 17:402–410
7. Serizawa S, Miyamichi K, Takeuchi H, Yamagishi Y, Suzuki M, Sakano H (2006) A neuronal identity code for the odorant receptor-specific and activity-dependent axon sorting. Cell 127:1057–1069
8. Spors H, Wachowiak M, Cohen LB, Friedrich RW (2006) Temporal dynamics and latency patterns of receptor neuron input to the olfactory bulb. J Neurosci 26:1247–1259
9. Verhagen JV, Wesson DW, Netoff TI, White JA, Wachowiak M (2007) Sniffing controls an adaptive filter of sensory input to the olfactory bulb. Nat Neurosci 10:631–639
10. Salcedo E, Zhang C, Kronberg E, Restrepo D (2005) Analysis of training-induced changes in ethyl acetate odor maps using a new computational tool to map the glomerular layer of the olfactory bulb. Chem Senses 30:615–626

Odor Memory

►Olfactory Perceptual Learning

Odor Perception

Definition

The ability to detect and recognize an odor

►Olfactory Perception
►Olfactory Sense

Odor Receptor

►Odorant Receptor

Odor Recognition

Definition

The perceptual process by which an odor sensation is cognitively related to its source or, in humans, by which an odor sensation evokes a verbal label that designates its source. In theory, odor recognition occurs at the recognition threshold, that is when a odor stimulus reaches the quantitative level at which it can be qualitatively recognized.

►Olfactory Perception

Odor Representation

►Odor Coding

Odor Sampling

Definition

Active exploration of an odor including acceleration of respiratory rhythm called sniffing behavior.

►Odor-sampling Behavior

Odor-Sampling Behavior

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Synonyms

Sniffing behavior (mammals); Wing fanning (insects); Flicking behavior (crustaceans); Coughing (fishes)

Definition

Odor-sampling designates a behavior by which animals actively collect air-borne or water-borne odor stimulus carrying information from the surroundings, in order to localize and/or identify the source of the emitted odor, and to respond in an adaptive manner (e.g. approach, avoidance) to the stimulation. To collect the odor stimulus, the organism may sniff, flick, fan, cough or bubble (according to the species and the environment), behaviors that consist in the active drive of air or water across or into the olfactory organ (sniffing, fanning, nasal sac compressing - coughing -, bubbling), or in the moving of the organ through the fluid carrying the stimulus (flicking).

Characteristics

Environment as a World of Odors

In the animal kingdom, odors are important vectors of information likely to elicit behavioral decisions supporting adaptive responses to social and feeding needs. Thus, from early to late development, olfaction is involved in detection and localization of, and communication with, conspecifics, detection of competitors and predators, selection of habitats, localization of preys and more generally of food.

However, animals are only intermittently exposed to odor stimuli. Indeed: (i) the olfactory organ (e.g. nose, antenna) is a structure which anatomically protects the substructures carrying the olfactory receptors, and therefore limits or blocks the continuous access of odor molecules to the receptors; (ii) informative odor cues (signals) are often sporadically emitted from odor sources spatially dispersed; (iii) odors are transported in the environment by wind or water currents submitted to physical turbulences (i.e. odors generally consist of plumes, patches or filaments in aerial and marine environments). In other words, odors in the ambient air or water are fluctuating both temporally and spatially. This creates the necessity for animals to sample their olfactory environment, i.e. to extract and gain access to the odor cues. Odor-sampling behavior responds to this necessity, in allowing a voluntary (intermittent) exposure to specific and ephemeral olfactory information emanating from the surroundings. In addition, odor-sampling behavior, coupled to the olfactory organ morphology, may form the first level of signal filtering, before its processing at the receptor then neural levels.

Odor-Sampling Behavior in Terrestrial Environment

In humans, and mammals in general, odor-sampling that follows the detection of an odor is supported by a so-called “sniffing” behavior. During a sniff, air enters through the nostrils (anterior nares), and continues through the nasal cavity, then out the posterior nares to the top of the throat. Part of the airflow reaches the

olfactory epithelium, which lines the roof of the nasal cavity (below the cribiform plate). Usually, a single human sniff approximately has a duration of 1.6 s, an average inhalation velocity of 30 l/min (twice that of a normal inspiration), and a volume of 500 cm^3. However, humans generally take several successive sniffs to sample odors, thus displaying sniffing episodes rather than single sniffs. During an episode, each sniff has a reduced duration and volume as compared to a single sniff, but the average inhalation velocity remains the same. Multiple sniffs are quite surprising knowing that odor presence and intensity can be determined, in laboratory conditions, in a single sniff. But sniffing episodes are certainly necessary in natural conditions, where the localization, identification and discrimination of odors constitute difficult tasks due to air turbulences and exposure to complex mixtures (emanating from biological sources) [1]. Human odor-sampling may for instance impact scent-tracking abilities, and is correlated with food neophobia.

In rodents, nostrils act as flow diverters during sniffing, permitting to inspire air from the immediate front of the snout and to expire it backward. Such aerodynamics makes sense, allowing extracting odor cues from the environment while reducing the disturbance of the olfactory sample. The sniffing behavior by itself consists in a relatively stereotyped sequence divided in two successive phases. During the first phase, the animal fixes the head, protracts the vibrissae, inhales briefly, and retracts the tip of the nose. Then, during the second phase, it retracts the vibrissae, exhales and protracts the nose. Generally, the entire sequence is repeated, after repositioning of the head, at around 4–12 Hz and occurs in bouts lasting 1–10 s. Sniffing behavior is considered to be synchronized with whisking, head bobbing and heartbeat. Recently, it was suggested to be constituted, in rats, by two successive modes: type-I sniffing, displayed with a respiration frequency of 6–9 Hz, allowing the acquisition of odor information; then type-II sniffing (9–12 Hz), preparing the animal to display the behavioral response accompanying its final decision [2].

In insects, olfactory receptors are borne by chemosensory sensilla carried by the antennae. Usually, the sensilla form a dense boundary layer between the whole antennae and the receptors. To sample odors from the surroundings, animals display particular wing motions that induce pulses of air flowing to the body, from front to rear. The consequence is an increase in the interception of chemical signals on the olfactory sensilla, due to a decrease in the depth of the boundary layer. Typical wing motions allowing such sampling happen during flight (these motions differ in angle and amplitude from those typically used to fly), or during walking in flying and non-flying insects. Wing motions displayed by walking insects to sample odors are named "wing fanning". This latter behavior severely increases the air penetration and rate of interception of odorant molecules both into the antennae and the sensilla: in silkworm moth (*Bombyx mori*), the airflow produced is 15 times faster at the level of the antennae, and 560 times faster at the level of the sensilla [3], as compared to walking.

Whatever the species, and in addition to the increase in the capture rate of odorants, sniffing and wing fanning may also have a second function: to replace the fluid volume being sampled, i.e. the fluid volume adjacent to the surface of the chemosensory structures. Both functions may occur with a single increase in velocity of airflow, or with periodic fluctuations in velocity (thus minimizing ►habituation and ►familiarization processes) [3].

Odor-Sampling Behavior in Aquatic Environment

Among arthropods, crustaceans present adaptations illustrating odor-sampling behavior. Crustaceans have different chemosensory organs, among which the lateral flagella of the first antennae (lateral antennules) constitute olfactory organs. In the American lobster (*Homarus americanus*) and Spiny lobster (*Panulirus argus*), for instance, olfactory sensilla (called aesthetascs) form a dense "toothbrush" on the distal half of the antennules. The brush forms, as in insects, a boundary layer which shields the receptors from odor access. When they perceive a chemical signal, lobsters generally wave their antennae and increase the rate of "antennule flicking" (the right and left antennules may flick independently). This behavior allows water to be driven at high velocity through the brush, the boundary layer to be decreased, and then stimulus access to the chemoreceptors (carried by the antennules) to be increased. In other words, antennular flicking is a form of "sniffing" in this taxon, and allows odor perception. It constitutes a behavioral expression which can be easily quantified, and which is therefore used to determine the biological relevance of stimuli. Antennular flicking is critical for efficient orientation behavior [4].

In fishes, odor-sampling behavior has often been thought to be relatively involuntary. In teleostean fishes, olfaction occurs when the water flow is sufficient to bring odor molecules in contact with the receptors embedded in the ciliated olfactory epithelium. The epithelium is located in two nasal sacs (situated in the dorso-anterior part of the head) opened by one or two nares. "Passive" increase of the water flow is induced by ciliary action of cells from the epithelium and by the increase in swimming speed (isosmate fishes), or by continuous pumping in the nasal chambers related to respiration (cyclosmates). However, voluntary sniffing behavior, named "coughing", has also been suggested. In pleuronectid flounders (e.g. *Lepidopsetta bilineata*, *Platichthys stellatus*; cyclosmates), coughing

consists in the rapid protrusion of the jaw, coupled with an expulsion of water from the mouth and an entrance of water in the nasal chambers through the nares. Then, the mouth closes, and water is rapidly expulsed from the nares. This behavior is usually displayed into a stereotyped behavioral sequence including the lift of the head off the substratum, and the orientation to the odor source. Coughing is, for instance, strongly displayed in response to food odorants. It is suggested to support voluntary and frequent sampling of small odorant patches, allowing to gain access to specific odor cues more efficiently than through the continuous circulation of water tied to respiration. Coughing may also have another function: the ejection of foreign material from the olfactory chambers or gills [5].

Finally, it is generally considered that mammals cannot sniff and smell in aquatic environment (except fetuses in the womb) since they are not able to inspire air. However, a recent study brings evidence that in semi-aquatic mammals, a particular mechanism may allow to sample odor underwater: the star-nosed mole (*Condylura cristata*) and the water shrew (*Sorex palustris*) are indeed able to exhale air bubbles onto objects or scent trails before re-inspiring these bubbles. The re-inspiration brings back into the nose the smell of the environmental targets contacted through the bubbles. Interestingly, the volume of air corresponding to these bubbles, the rate of airflow and the frequency characterizing this behavior appear similar to that related to sniffing in small rodents living above water. Such underwater sampling behavior can therefore be considered equivalent to sniffing in the air [6].

Functional Aspects of Odor-Sampling

Odor-sampling behavior is not only dedicated to the transport of odorants from the environment to the olfactory receptors. It is a dynamic process which directly participates in the temporal and spatial coding of odor stimuli. More generally, it constitutes a main component of olfactory processing and influences olfactory percept. For instance, in humans, functional magnetic resonance imaging (fMRI) demonstrates that odor-sampling (sniffing) induces activity in the primary olfactory cortex, and that this activation reflects the encoding of air flow as a factor contributing to the computation of odor intensity and identity [7].

The changes in air flow induced by sniffing through the nasal cavity (in mammals) could influence the mechanical component of the odor perception: in the olfactory epithelium, olfactory neurons detect the chemical but also mechanical stimulation caused by odorant molecules. Regarding the olfactory perception per se, variations in air flow result first in distinct retention of the odorants carried by the flow, and therefore in distinct perception. Thus, high or low velocities respectively optimize perception of odorants presenting higher, or lower, sorption rate. Second, the air flow related to sniffing also influences the distribution of odorant molecules over the epithelium. By the way of this active mechanism, distinct odorants are spatially directed to distinct regions of the nasal cavity and to different populations of olfactory receptors, a process called "zonation" [8]. Subsequently, sniffing impacts the spatial representation of an odor at the level of the olfactory bulb, and influences the detection, identification, and discrimination abilities of animals.

Moreover, sniffing behavior carries temporal information about volatile cues throughout the olfactory system, from the olfactory bulb to higher cerebral structures. This impact is important knowing that temporal properties of an odor cue contribute to its representation. From this point of view, electrophysiological recordings reveal that odor-related activity in the olfactory bulb is strongly modulated by respiration and that the phase of spiking relative to the sniff cycle might encode information regarding odorant intensity and quality. Interestingly, the slow theta rhythm (4–12Hz in rats) generally recorded during sniffing in the mitral cell layer of the bulb, is also observed in the hippocampus, a structure involved in memory and orientation behavior. Such coherence in frequency between distinct brain areas might illustrate the cooperation of sensory, motor and cognitive cerebral regions expressed when the animal is engaged in an adaptive task. For instance, theta oscillations are both displayed in the olfactory bulb and dorsal hippocampus of rats that are sniffing during the initial stages of a reversal odor learning [9].

Finally, in complex natural scenes, sniffing plays a role in odor perception through successive sniffing cycles (even if a single sniff supports odor detection and identification). Successive samplings participate in progressive change of olfactory network dynamics which may then lead to a might converge, by the repetition of sniffing actions, in a more precise odor representation. From this point of view, multiple sniffs compose a synthetic memory-based system forming "perceptual gestalts" [10], which might be determinant for analysis of complex olfactory mixtures, identification of relevant odor cues and scent-tracking.

References

1. Laing D (1983) Natural sniffing gives optimum odor perception for humans. Perception 12:99–117
2. Kepecs A, Uchida N, Mainen ZF (2007) Rapid and precise control of sniffing during olfactory discrimination in rats. J Neurophysiol 98:205–213
3. Loudon C, Koehl MAR (2000) Sniffing by a silkworm moth: wing fanning enhances air penetration through and pheromone interception by antennae. J Exp Biol 203:2977–2990
4. Atema J (1995) Chemical signals in the marine environment: Dispersal, detection, and temporal signal analysis. Proc Natl Acad Sci USA 92:62–66

5. Nevitt GA (1991) Do fish sniff? A new mechanism of olfactory sampling in pleuronectid flounders. J Exp Biol 157:1–18
6. Catania KC (2006) Underwater "sniffing" by semi-aquatic mammals. Nature 444:1024–1025
7. Mainland J, Sobel N (2006) The sniff is part of the olfactory percept. Chem Senses 31:181–196
8. Schoenfeld TA, Cleland TA (2006) Anatomical contributions to odorant sampling and representation in rodents: zoning in on sniffing behavior. Chem Senses 31:131–144
9. Macrides F, Eichenbaum HB, Forbes WB (1982) Temporal relationship between sniffing and the limbic theta rhythm during odor discrimination reversal learning. J Neurosci 2:1705–1717
10. Wilson DA (2001) Receptive fields in the rat piriform cortex. Chem Senses 26:577–584

Odor Selectivity

Definition

Property of neuron responses (firing rate or other measure of odor response) that varies dependent on the odorant stimulus.

►Olfactory Information

Odor Tracking (Localization)

Definition

The chain of motor actions by which animals search and efficiently orient to a source of odor cues over short or long distances. The recipient organism displays general body movements (as in male moth approaching a female) or local head movements (as in mammalian newborns locating the mother's nipple) to create sensory asymmetry in the plumes released by an odor source in order to stimulate chemosensors located in or on bilateral organs (antennae, nasal fossae).

►Social Chemosignal

Odorant

Definition

An odorant is a volatile chemical molecule that that naturally exists as a component of an odor.and is sensed by the olfactory system. Odorants stimulate sensory neurons of the olfactory system in the nasal cavity by binding to odorant (olfactory) receptor proteins on the cell membrane, triggering an electrical response that can be transmitted to the brain. The ability of an odorant to bind to and activate an olfactory receptor protein depends on molecular features such as the size, shape and presence of functional groups. Naturally occurring odors may be composed of hundreds of odorants.

►Glomerular Map
►Memory – Odor
►Odorant Receptor Protein
►Odor
►Olfactory Perceptual Learning

Odorant-Binding Proteins

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Synonyms

Odor-binding proteins; Olfactory binding proteins

Definition

Odorant-binding proteins (OBPs) are abundant small soluble proteins secreted in the ►nasal mucus of a variety of species, from insects to vertebrates including human beings. OBPs reversibly bind odorants with dissociation constants in the micromolar range and are good candidates for carrying airborne odorants, which are commonly hydrophobic molecules, through the aqueous nasal ►mucus towards olfactory receptors. Although the physiological function of vertebrate OBPs is not yet clearly established, their essential role in eliciting the behavioral response and odor coding have been demonstrated in the fruit fly [1].

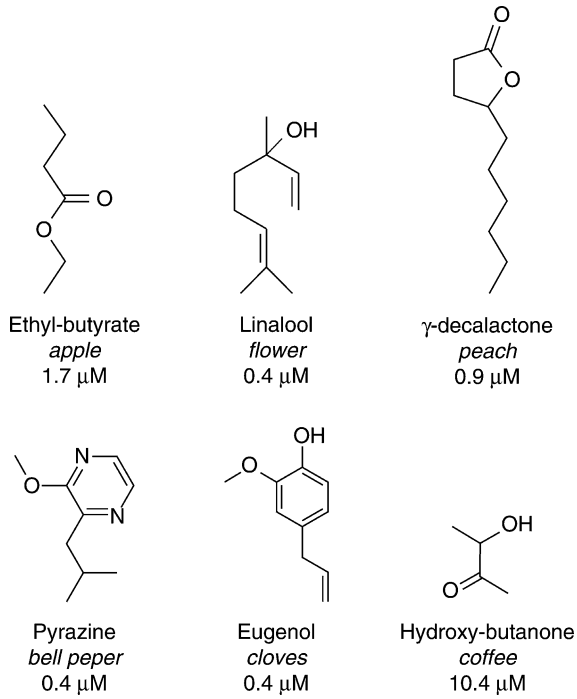
Characteristics

General Properties of Vertebrate Obps

OBPs are secreted by the olfactory epithelium in the nasal ►mucus at high concentration (~10 mM). They reversibly bind odorants with dissociation constants in the micromolar range [2]. OBPs have been identified in a variety of vertebrates including cow, pig, rabbit, mouse, rat, xenopus, elephant and human beings [2–4]. Different OBP subtypes have been reported to occur simultaneously in the same animal species, two in pig, four in mouse, three in rabbit and at least eight in

porcupine. In rat, three OBPs have been cloned with quite different sequences and binding properties [5]. Molecular weights of OBPs fall within a narrow range (around 18 kDa). They are highly soluble proteins belonging to the lipocalin superfamily. As regards their quaternary structure, some OBPs were observed as monomers, such as porcine, rat OBP-3 or human OBP, while some others are found as dimers, such as bovine OBP, rat OBP-1 and OBP-2. OBP heterodimers have also observed in mouse. The typical isoelectric point of OBPs is in the acidic range, between 4 and 5. However, some rare OBPs exhibit a neutral or slightly basic isoelectric point, such as rat OBP-2 and human hOBP-2A. As sites of production, OBPs are synthesized within the nasal cavity, but in different glands and areas. Some OBPs have been clearly shown to be expressed in the olfactory area by the Bowman's glands.

OBPs are also found in the sensillary lymph of insect antennae. Although insect OBPs seem to play a similar role in olfaction, they do not share any amino acid sequences or structural similarities with vertebrate OBPs [5].



Odorant-Binding Proteins. Figure 1 Examples of odorants presenting different odors, which bind tightly or weakly to rat OBP-1. The dissociation constants of these compounds for rat OBP-1 are indicated in italics.

Human OBPs

Two putative human OBP genes (named $hOBP_{IIa}$ and $hOBP_{IIb}$) localized on chromosome 9q34 were first described before evidence of human OBP expression in the mucus covering the olfactory cleft [4]. The $hOBP_{IIa}$ gene codes for a protein, called hOBP-2A, which is 45.5% homologous to rat OBP-2. This gene is transcribed in the nasal cavity, in contrast to$hOBP_{IIb}$, which is transcribed in the genitals and codes a protein that is 43% identical to the human tear lipocalin-1. The presence of human OBP expression appears limited to the uppermost region of the ►nasal passage where odorant molecules are detected by olfactory receptor neurons.

Ligand Binding Properties of OBPs

OBPs bind with high efficiency a large number of odorants belonging to different chemical classes (Fig. 1).

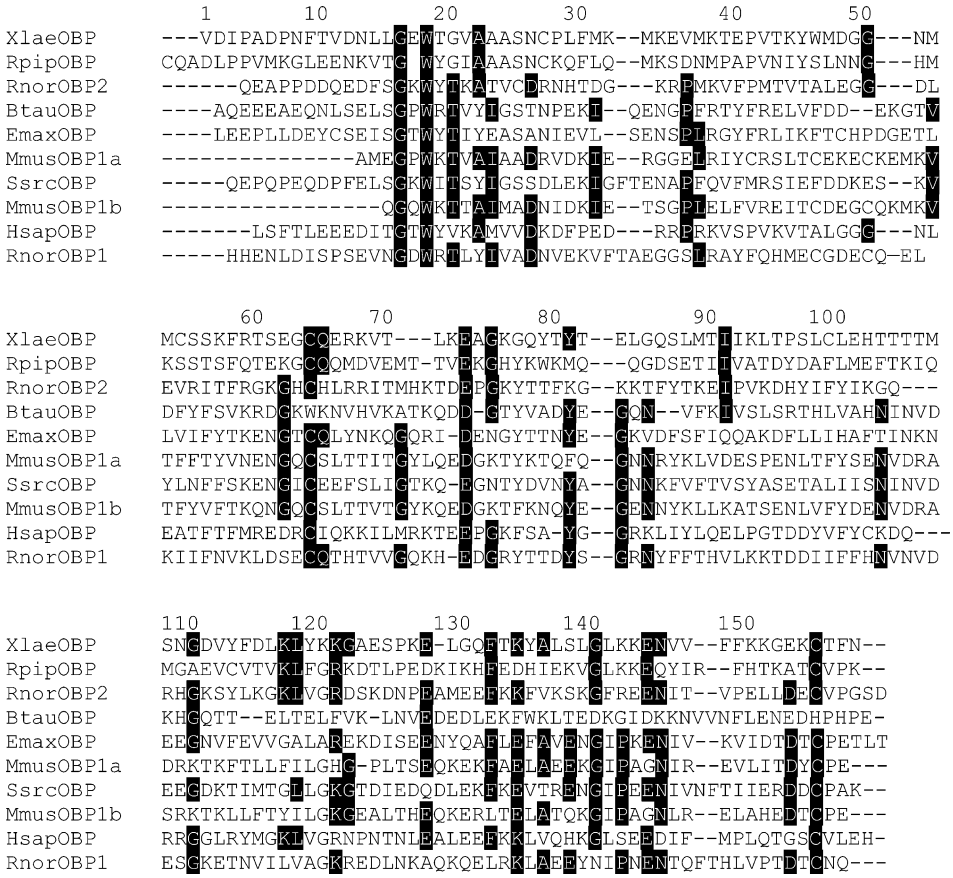
Although no preferential binding was observed with the porcine and bovine OBPs, a broad specificity was revealed by the study of the 3 rat OBPs, which are specially tuned towards distinct chemical classes of odorants. Rat OBP-1 preferentially binds heterocyclic compounds such as pyrazine derivatives and OBP-2 appears to be more specific for long-chain aliphatic aldehydes and carboxylic acids, whereas OBP-3 was described to interact strongly with odorants composed of saturated or unsaturated ring structure [6].

Human OBP-2A was observed to bind many diverse odorants with dissociation constants in the micromolar range, as found in all known vertebrate OBPs [4]. However, specificity of hOBP-2A is more restricted than those of porcine and rat OBP-1 and 3. A chemical specificity of this OBP for aldehydes, either aliphatic or aromatic, enhanced by the size of the odorant molecule, ir clear comparing odorant chemical series. Note that hOBP-2A can also be characterized by its low affinity for a very potent odorant, 2-isobutyl-3-methoxy pyrazine, and a very high affinity for large aliphatic acids.

Consensus Sequence, Homology and Disulfide Bond

All known vertebrate OBPs belong to the lipocalin superfamily. All members of this family have low sequence identity, but few characteristic signatures allow their identification: a GxW motif at about 15–20 residues from the N-terminus, two cysteines in the middle and a glycine at the C-terminal end (Fig. 2).

One of the conserved cysteine residues, located on the fourth strand of the first β-sheet, forms a disulfide bridge tightening the α-helix C-terminal domain and the β-barrel. When comparing OBP sequences, note that the percentage of identity among OBPs is low (21–26% on average) with the bovine and porcine OBP showing a maximal identity (42%), whilst rat OBP-2 exhibits the lowest identity (12–19%) when compared to all other OBPs. Consequently, tissue expression (i.e. in the olfactory epithelium) and ligand binding properties should be systematically taken into account in order to classify OBPs.



Odorant-Binding Proteins. Figure 2 Sequence alignments of vertebrate OBPs. Conserved amino acid residues are shown white on black background. OBPs are: XlaeOBP (*Xenopus laevis* OBP), RpipOBP (*Rana pipiens* OBP), RnorOBP1 (Rat OBP-1), RnorOBP2 (Rat OBP-2), MmusOBP1a (Mouse OBP subunit IA), MmusOBP1b (Mouse OBP-1B), BtauOBP (Bovine OBP), EmaxOBP (Elephant OBP), SsrcOBP (Porcine OBP) and HsapOBP (Human OBP-2A).

Structural Properties of OBPs

Vertebrate OBPs like other members of the lipocalin superfamily display low sequence similarities, but share a conserved folding pattern made of an 8-stranded antiparallel β-barrel linked together by seven loops, and connected to an α-helix (Fig. 3). The β-barrel defines a central apolar cavity, called the calyx, whose role is to bind and transport hydrophobic molecules such as odorants [3].

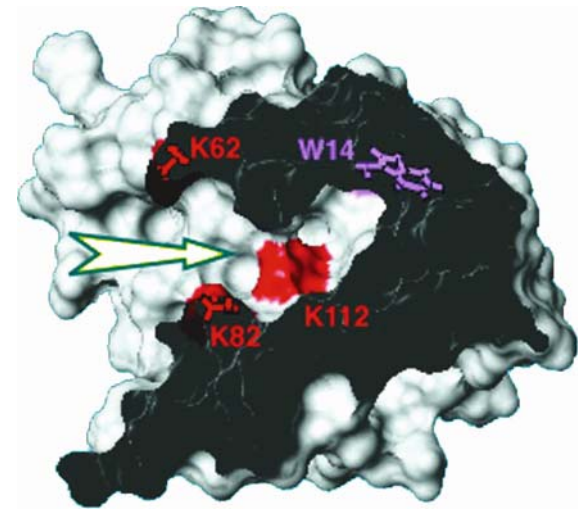
Bovine OBP, which forms a dimer with an elongated shape, was the first OBP whose structure was deciphered through X-ray crystallography [7] and was therefore considered as the prototype of OBP, in spite of the absence of the second disulfide bridge. However, the molecule is not a classical lipocalin, since it exhibited a structural feature called domain swapping. The β-barrel of each monomer comprises its own strands 1–8, but the eighth strand originates from the other monomer. By this mechanism, the C-terminal part of one of the homodimers rotates and takes the place of that of the other. In addition to the buried cavity in the middle of the β-barrel, as in monomeric OBPs, a central pocket, composed of residues belonging to the β-barrel domains and to the C-terminal ends, is located at the dimer interface in communication with the solvent.

Porcine OBP is a monomer whose 3D-structure is typical of a lipocalin. Two cysteine residues form a disulfide bridge between the C-terminal and the loop joining strands 3 and 4 of the β-barrel [8] and a single cavity is observed inside the β-barrel, which does not communicate directly with the external solvent. A few amino acid side chains, which block the access to the solvent, would therefore have to move to make the binding of odorants possible. The cavity is mainly covered with hydrophobic and aromatic side chains.

Structure of the Odorant-Binding Pocket

Up to now, only a few odorant-OBP complexes have been submitted to structural analysis. It has been observed that two odorant molecules could occupy

Odorant-Binding Proteins. Figure 3 Ribbon representation of porcine OBP-1 forming a typical lipocalin eight-strand β-barrel, flanked by a single α-helix. The color coding is according to the secondary structure; helices, red; L-strands, cyan; other motifs, green.



Odorant-Binding Proteins. Figure 4 Slabbed view through the molecular surface and binding-pocket of the predicted 3D-structure of human OBP-2A. In the binding-pocket (*arrow*), lysine side chains and surfaces are colored in red, tryptophan in violet.

the β-barrel cavity of bovine OBP [8]. On the basis of porcine OBP data [9], the most likely binding site is inside the β-barrel, since this may be general for all OBPs. The size of the β-barrel pocket was found to be 780 $Å^3$ [8] for the bovine protein and about 500–550 $Å^3$ for the porcine OBP [9]. Using porcine OBP, a limited number of odorants, with relatively good affinity (affinity constants $> 10^6$ M^{-1}) and different chemical groups (aromatic ring, aliphatic chain or polar group) were co-crystalized with porcine OBP [9]). In the crystalline complexes, the odorant orientation inside the cavity have been proved to be opportunistic with no specific target patches for aromatic or charged group. Interactions between the different odorants and the β-barrel involve most of the residues in the cavity. Except for the two asparagines, which display a polar interaction between the amino acid side chain and the keto oxygen of benzophenone, all interactions are hydrophobic. The number of these interactions appears to be roughly related to the size of the odorant, but without any correlation with affinity measured in solution. Although the odorant-binding pocket is shielded from the solvent, openings have been observed using molecular simulations and it has been proposed that, tyrosine residue Y82 constitutes the door of the cavity. As regard human OBP-2A, its three-dimensional structure have not been yet described but a model has been proposed (Fig. 4). It has been shown using site-directed mutagenesis that affinity enhancement of OBP-2A for aldehydes compared to the corresponding aliphatic acids, could result from an interaction between aldehyde function and lateral chain of a lysyl residue K112, stabilizing odorant docking [10].

Hypothetical Physiological Functions

In mammals and in insects, olfactory receptors are separated from air by a protective layer of hydrophilic secretion, the nasal mucus and sensillar lymph, respectively. Hydrophobic airborne odorants have to cross this aqueous barrier to reach their neuron receptors. OBPs, which have been hypothesized to play such a transporter role, likely appeared during the adaptation to terrestrial life. This carrier role is also supported by their relatively low affinity constant for odorants associated with their high concentration in the olfactory fluids. Their involvement in olfactory discrimination has also been proposed, because of the presence in the mucus of rat of three different OBP subtypes, specifically tuned toward distinct chemical classes of odorants [6]. In addition to the solubilization of odorants, various hypotheses have been proposed for other OBP functions [2]. They could either, (i) filter and buffer odorants in the mucus, then narrow the wide range of odorant intensities, (ii) eliminate odorants after olfactory receptor binding, or (iii) directly interact with olfactory receptors. The essential role of OBPs in eliciting the behavioral response and coding of odor has only been demonstrated in insects. It has been demonstrated that drosophila OBP LUSH is mandatory for the activation of pheromone-sensitive chemosensory neurons [1]. In mammals, it is stimm a

matter of debate whether there might be involved ►specific anosmia or ►parosmia.

References

1. Xu P, Atkinson R, Jones DN, Smith DP (2005) *Drosophila* OBP LUSH is required for activity of pheromone-sensitive neurons. Neuron 45:193–200
2. Pelosi P (2001) The role of perireceptor events in vertebrate olfaction. Cell Mol Life Sci 58:503–509
3. Tegoni M, Pelosi P, Vincent F, Spinelli S, Campanacci V, Grolli S, Ramoni R, Cambillau C (2000) Mammalian odorant binding proteins. Biochimica et Biophysica Acta 1482:229–240
4. Briand L, Eloit C, Nespoulous C, Bezirard V, Huet J-C, Henry C, Blon F, Trotier D, Pernollet J-C (2002) Evidence of an odorant-binding protein in the human olfactory mucus: location, structural characterization, and odorant-binding properties. Biochemistry 41:7241–7252
5. Tegoni M, Campanacci V, Cambillau C (2004) Structural aspects of sexual attraction and chemical communication in insects. Trends Biochem Sci 29:257–264
6. Löbel D, Jacob M, Volkner M, Breer H (2002) Odorants of different chemical classes interact with distinct odorant binding protein subtypes. Chem Senses 27:39–44
7. Tegoni M, Ramoni R, Bignetti E, Spinelli S, Cambillau C (1996) Domain swapping creates a third putative combining site in bovine odorant binding protein dimer. Nat Struct Biol 3:863–867
8. Spinelli S, Ramoni R, Grolli S, Bonicel J, Cambillau C, Tegoni M (1998) The structure of the monomeric porcine odorant binding protein sheds light on the domain swapping mechanism. Biochemistry 37:7913–7918
9. Vincent F, Spinelli S, Ramoni R, Grolli S, Pelosi P, Cambillau C, Tegoni M (2000) Complexes of porcine olfactory-binding protein with odorant molecules belonging to different chemical classes. J Mol Biol 300:127–139
10. Tcatchoff L, Nespoulous C, Pernollet JC, Briand L (2006) A single lysyl residue defines the binding specificity of a human odorant-binding protein for aldehydes. FEBS Lett 580:2102–2108

Odorant Receptor

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Synonyms

Olfactory receptor; Odor receptor; Olfactory receptor protein; OBPs

Definition

►Odorant receptor proteins are G protein-coupled seven transmembrane proteins, which number more than 1,000 in some mammalian species, and mediate the detection of thousands of volatile odorants. They are expressed, in mammals, in the cilia of the olfactory sensory neurons residing in the olfactory neuro-epithelium in the nasal cavity. They are located, in adult insects, on either the antennae or maxillary palp. They are expressed by sperm cells, and are thought to trigger ►chemotaxis toward the oocyte. A second class of odorant receptor proteins was described in 2001 for volatile amines, and called "trace amine-associated receptors" (TAAR). Most odorant receptors recognize multiple related odors and most odorants are recognized by several receptors.

Characteristics

Quantitative Description

In 1991, Buck and Axel discovered the odorant receptor gene family in rat [1]. In 2004, Linda Buck and Richard Axel won the Nobel Prize in Physiology or Medicine for this major discovery. Odorant receptors are seven-transmembrane-domain proteins encoded by large gene families. *Drosophila* has a highly diverse family of 60 odorant receptor genes [2]. In mammals, the odorant receptor family of genes, comprising some 1,100 functional genes in the mouse, 347 in the human, respectively, is the largest family of G protein-coupled receptors in the genome, which may make up as much as 3% of the genome. Only a small part of odorant receptor genes form functional ►odor receptors. In the mouse, 1,296 odorant receptor genes (including 20% pseudogenes) were found, which can be classified into 2,228 families [3]. Mouse odorant receptor genes are distributed in 27 clusters on all mouse chromosomes except 12 and Y. The distribution was not uniform, with more than half of the genes contained in a few large, compact clusters on chromosomes 7, 11 and 9. Class I odorant receptors correspond to fish-like receptors that bind water-soluble odorants, and separate clearly in the phyllogenetic tree from the classical, mammalian-specific class II odorant receptors. There are 147 Class I odorant receptors in the mouse odorant receptor subgenome, 120 of them potentially functional. All the class I odorant receptor genes are located in a single large cluster on chromosome 7 (cluster 7–3). Class I odorant receptors are prevalent in the mammalian genome and may be centrally involved in mammalian olfaction. In the mouse, they are expressed in the most dorsal zone of the olfactory epithelium. Conversely, Class II receptors have been found in all four zones.

Humans have lost nearly two-third of the odorant receptor genes as compared to mice, providing a possible explanation for the reduced sense of smells of humans compared to rodents. The human odorant receptor genome repertoire is organized similarly to the mouse one [4]. Human odorant genes are dispersed in more than 50 chromosomal locations and organized mostly in clusters. Most subfamilies are encoded by a

single locus and most loci encode a single or very few subfamilies. Odorant receptors of a single locus recognize structurally related odorants, suggesting that different parts of the genome are involved in the detection of different odorant type.

A second class of odorant receptors was described in 2001 for volatile amines, metabolic derivatives of classical biogenic amines, and called 'trace amine-associated receptors' (TAAR). Encoding TAAR are present in human, mouse and fish olfactory neurons [5]. They show sequence similarities to the receptors for the neurotransmitters serotomin and dopamine. TAAR1 is thought to be a receptor for thyronamines, decarboxylated and deiodinated metabolites of the thyroid hormones, while the mouse mTAAR2- mTAAR9 receptors are most probably olfactory receptors for volatile amines.

Description of the Structure and Pharmacology

Odorant receptors are in every species heptahelical G-protein-coupled receptors. In mammals, odor receptors belong to class A of the G protein-coupled receptors that are characterized by a long second extracellular loop, containing an extra pair of conserved cysteins, and specific short sequences [6]. Odor receptors share a similarity from 40 to 90% identity. They also have a region of hypervariability, which is the binding site for ligands. This region consists in the third, fourth and fifth alpha – helical transmembrane regions, thought to face each other and form a pocket into the membrane. Mammalian odor receptors are related phyllogenetically to other chemosensory receptors (taste receptors, vameronsal receptors and gustatory receptors). Invertebrate odor receptors bear no homology to vertebrate odorant receptors. *Drosophila* odorant receptors have a mildly conversed region in the seventh transmembrane domain [2].

Odorant receptors bind to structures on odor molecules. They are generally able to recognize multiple related but not identical molecules. They are able to discriminate between thousands of low molecular mass, aliphatic and aromatic molecules with varied carbon backbones and diverse functional groups, including aldehydes, esters, ketones, alcohols, alkenes, carboxylic acides, amines, imines, thiols, halides, nitriles, sulphides and ethers. For many odors, the dose-response curves in single cells have relatively elevated EC50 values, or midpoint, ranging from 10 to 100 μM. They can be activated by multiple odors, and conversely most odors are able to activate more than one type of receptor.

Members of the TAAR family are activated by the trace amines found in the central nervous system (beta-phenylethylamine, tyramine, tryptamine and octopamine). Individual TAAR are specific for different amine structures; three of them are activated by volatile amines found in urine (a source of pheromonal cues of a variety of chemical compositions), some of which have been involved in regulating reproductive behavior [5].

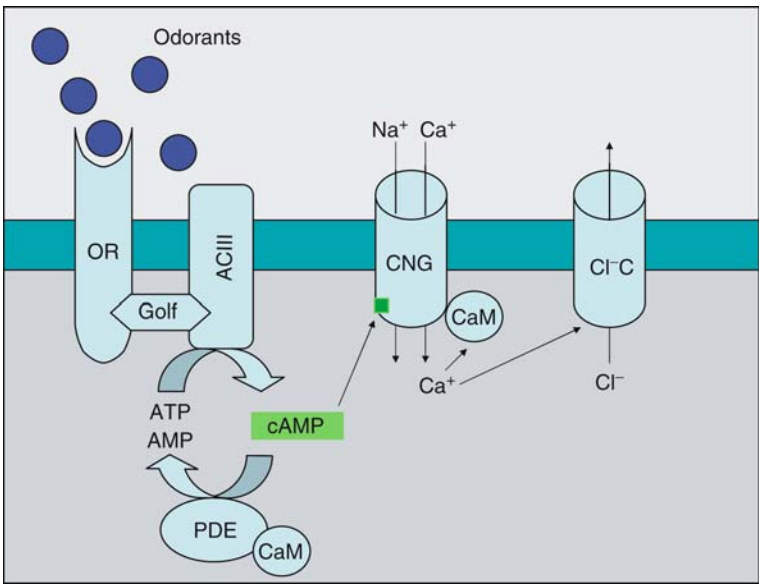
Olfactory Signal Transduction

Odorant receptors are specialized to detect certain odorants and to convert external stimuli into intracellular signals [7]. Once the odorant has bound to the odorant receptor, the receptor undergoes structural changes and sequentially activates the specific olfactory-type G protein (Golf) and the lyase – adenylate cyclase type III (ACIII)- which converts ATP into cyclic AMP (cAMP), a molecule that has numerous signaling roles in cells. See Fig. 1.

The cAMP opens specific cyclic nucleotide-gated (CNG) channels, which allow calcium and sodium ions to enter into the cell, depolarizing the ►olfactory sensory neuron and triggering action potentials which then carry odor information to the olfactory bulb in the brain. The second-messenger cascade of enzymes provides amplification and integration of odor-binding events. The binding of one odor molecule to an odorant receptor activates tens of Golf proteins, each of which will activate an adenylyl cyclase III molecule able to produce about a 1,000 molecules of cAMP per second. Three cAMP molecules are sufficient to open a CNG channel, which can allow the crossing of hundred of thousands of cations, depolarizing the cell and inducing an action potential. The calcium ions entering through the CNG channels are capable of activating and thus opening channels permeable to negatively charged chloride ion (Cl^-). When the Cl^- channels open, the Cl^- efflux further depolarizes the olfactory sensory neuron, thus adding to the excitatory response magnitude. On the other hand, calcium ions entering through the CNG channels act on these channels, probably with calmodulin, to decrease their sensitivity to cAMP, thus requiring a stronger odor stimulus to produce sufficient cAMP to activate the channels. This negative feedback (inhibitory) pathway constitutes a crucial adaptation response allowing olfactory sensory neurons to adjust their sensitivity to odor stimuli. In invertebrates, both excitatory and inhibitory responses to odors have been described, suggesting the existence of multiple transduction pathways.

Expression and Function

In insects, olfaction is a critical sensory modality for controlling behaviors such as mate selection, food choice and navigation toward suitable oviposition sites. Odorant receptors are located, in adult insects, in small subsets of olfactory receptor neurons in either the antenna or maxillary palps, which constitute the olfactory sensory organs. In mammals, the sense of smell is triggered by odorant receptors, which are expressed in the cilia of the olfactory sensory neurons of the olfactory neuroepithelium lining the nasal cavity. In mice, odorant receptors are also involved in mating and other social



Odorant Receptor. Figure 1 ►Olfactory transduction. Within the olfactory sensory neuron, a cascade of enzymatic activity transduces the binding of an odorant molecule to an odorant receptor into an action potential that can be transmitted to the central nervous system. OR, odorant receptor; ACIII, adenylyl cyclase III; CNG, cyclic nucleotide-gated channel; Cl−C, negatively charged clhoride ion channel; CaM, calmodulin; PDE, phosphodiesterase.

behaviors. Moreover, in mammals, a subset of odorant receptors is specifically expressed in the testis and odorant receptors have been identified in spermatids and mature spermatozoa [8]. These odorant receptors may play a role in chemotaxis of spermatozoa toward the oocyte.

In *drosophila*, each sensory neuron express only a single odorant receptor, and all sensory neurons expressing the same receptor contact a single restricted target, named ►glomerulus in a relay station called the antennal lobe of the brain, analogous to the vertebrate olfactory bulb. *Drosophila* has about 50 types of olfactory receptor neurons, corresponding to about 50 identified glomeruli in the antennal lobe [2].

In mammals, with a few exceptions, each olfactory sensory neuron expresses only one of the 1,000 odorant receptor genes [9]. All cells expressing the same receptor converge onto one or a few glomeruli, in the olfactory bulb [6]. Glomeruli (nearly 2,000 in the rat) are spherical conglomerate of neuropil (diameter of 50–100 μ) that consists of the incoming axons of the olfactory sensory neurons and the dendrites of the main projection cells (mitral cells) in the olfactory bulb. Mitral axons of olfactory sensory neurons leaving the olfactory bulb project to higher brain structures including the piriform cortex, the olfactory cortex, hippocampus and amygdala, allowing for both the conscious perception of odors and their emotional and motivational effects. Lateral processing of the message occurs though two populations of inhibitory GABAergic interneurons in the olfactory bulb: periglomerular cells and granule cells. Each glomerular unit presents a receptive field that is thought to be defined by the molecular range, or pharmacological profile of each odorant receptor.

The mammalian olfactory system uses a combinational receptor coding scheme to encode odor identity and to discriminate odors [10]. A given odor activates a set of odorant receptors, and then a set of olfactory sensory neurons, and then a set of glomeruli in the olfactory bulb, forming a spatial map of sensory information. Different odors activate overlapping but non-identical patterns of receptors and thus glomeruli. Slight changes in the structure of an odorant or changes in its concentration results in changes in the combination of receptors that recognize the odorant. Receptors that recognize similar odors (such as ►enantiomers) generally map in the same area in the olfactory bulb. Individual TAAR are sparsely expressed in discrete subdomains of the neuroepithelium, and are co-expressed with neither other TAAR, nor probably the odorant receptors. In mice, TAAR may mediate behavioral and physiological responses to amine-based social cues present in urine, as urine from sexually mature male mice, but not from females or sexually immature mices, could stimulate mTAAR5, a receptor activated by trimethylamine [5].

References

1. Buck L, Axel R (1991) A novel multigene family may encode odorant receptors: a molecular basis for odor recognition. Cell 65(1):175–187
2. Vosshall LB, Wong AM, Axel R (2000) An olfactory sensory map in the fly brain. Cell 102(2):147–159

3. Zhang X, Firestein S (2002) The olfactory receptor gene superfamily of the mouse. Nat Neurosci 5(2):124–133
4. Malnic B, Godfrey PA, Buck LB (2004) The human olfactory receptor gene family. Proc Natl Acad Sci USA 101(8):2584–2589
5. Liberles SD, Buck LB (2006) A second class of chemosensory receptors in the olfactory epithelium. Nature 442(7103):645–650
6. Mombaerts P (1999) Seven-transmembrane proteins as odorant and chemosensory receptors. Science 286(5440):707–711
7. Firestein S (2001) How the olfactory system makes sense of scents. Nature 413(6852):211–218
8. Spehr M, Gisselmann G, Poplawski A, Riffell JA, Wetzel CH, Zimmer RK, Hatt H (2003) Identification of a testicular odorant receptor mediating human sperm chemotaxis. Science 299(5615):2054–2058
9. Serizawa S, Miyamichi K, Nakatani H, Suzuki M, Saito M, Yoshihara Y, Sakano H (2003) Negative feedback regulation ensures the one receptor-one olfactory neuron rule in mouse. Science 302(5653):2088–2094
10. Malnic B, Hirono J, Sato T, Buck LB (1999) Combinatorial receptor codes for odors. Cell 1999 96(5):713–723

Odorant Receptor: Genomics

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Definition

►Odorant receptor genomics refers to the study of the structure and function of genes encoding receptors involved in the sense of smell. It includes defining the number and chromosomal arrangements of odorant receptor genes present in various genomes, as well as the molecular mechanisms that regulate their expression in an organism.

Characteristics

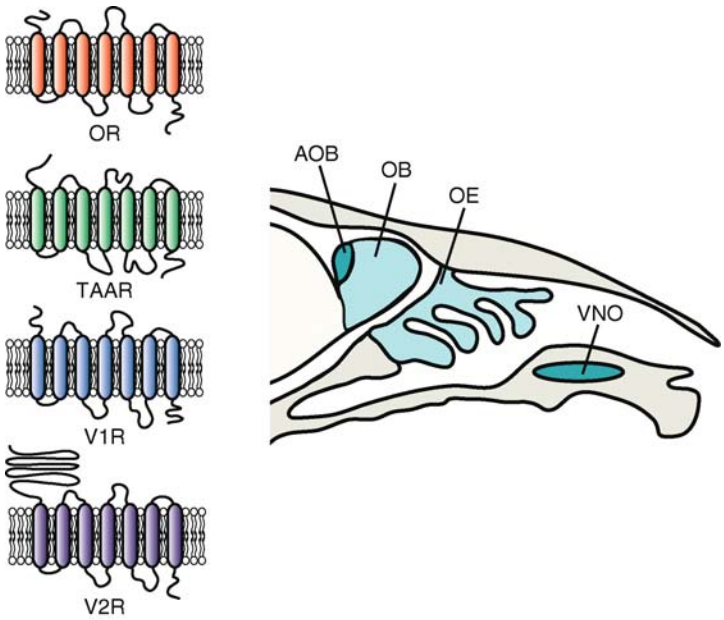
The survival and well being of most terrestrial vertebrates is dependent on their ability to detect ►odors in their environment and to respond to social cues. Neurons located in sensory epithelia of the nasal cavity detect volatile and water-soluble molecules and transmit the information gathered to the brain where it is further processed to generate odor perception and behavioral outputs. While the detection of volatile odorant molecules plays an important role in the modulation of acquired behavior such as food foraging, detection of ►pheromones is thought to control innate responses such as male-to-male aggression in many vertebrate species. The ►olfactory epithelium (OE) contains olfactory sensory neurons that express two classes of ►chemosensory receptors: the odorant receptors (ORs) and the trace amine-associated receptors (TAARs). While ORs recognize odor molecules, TAARs are proposed to detect compounds that can provide social cues. In contrast to the OE, the sensory epithelium of the vomeronasal organ contains sensory neurons that express two classes of putative pheromone receptors, the V1R and V2R families. Together, these families of seven-transmembrane G protein-coupled receptors (►GPCRs) allow organisms to detect a large range of molecules that regulate their behavior (Fig. 1).

Odorant Receptors (ORs)

The ability of terrestrial vertebrates to discriminate thousands of complex odors in the environment relies on the detection of odorant molecules by ORs. A single OR can recognize a multitude of odorant molecules and a specific odorant can bind to several ORs perhaps eliciting different levels of neuronal activity. The combination of ORs activated by odorant molecules present in a complex odor leads to the propagation of signals that ultimately renders a representation of the odor in the central nervous system. In light of the complexity of this ►combinatorial code, it is not surprising that ORs represent one of the largest mammalian gene families.

In some terrestrial vertebrates that rely heavily on their sense of smell for survival, such as the mouse, larger OR gene repertoires have been described than in humans whose sense of smell is considered to be more aesthetic. The mouse genome contains ~1400 genes that are organized in clusters located on almost all chromosomes [1]. While the majority of these genes encode functional ORs, ~15% of them are ►pseudogenes. The coding region of OR genes consists of a single ►exon preceded by an ►intron that separates it from non-coding exons in the 5′ region. The coding exon gives rise to OR proteins that are 300–350 amino acids in size. ORs contain structural features that are common to most GPCRs such as the seven hydrophobic stretches that form the transmembrane domains and specific conserved cysteines that form potential disulfide bonds. In addition, ORs contain sequences that distinguish them from other GPCRs including a long second extracellular loop, as well as conserved amino acid motifs in an intracellular loop and in some of the transmembrane domains. The presence of these conserved features in ORs are usually enough to classify a gene as belonging to the large family of ORs. Nonetheless, aside from these conserved features, there is on average an overall low amino acid similarity (37%) between ORs. This may allow the OR repertoire to recognize a large number of structurally diverse odorants.

The OR superfamily is subdivided into two classes of receptors. Class I ORs were originally identified in fish



Odorant Receptor: Genomics. Figure 1 Anatomy of the olfactory systems and structure of olfactory receptors. Olfactory sensory neurons located in the olfactory epithelium (OE) project axons that connect with second-order neurons in the olfactory bulb (OB). In contrast, vomeronasal neurons located in the vomeronasal organ (VNO) project their axons to the accessory olfactory bulb (AOB) where they form synapses with second-order neurons. The information processed by second-order neurons is relayed to various regions of the brain where an odor representation is generated. Olfactory receptors belong to the large family of G-protein coupled seven-transmembrane receptors. While odorant receptors (OR) and trace amine-associated receptors (TAAR) are expressed in the OE, two families of vomeronasal receptors (VR), V1R and V2R, are expressed in the VNO.

but later shown to represent approximately 10% of the mouse OR gene repertoire. In contrast, class II genes have so far been identified only in terrestrial vertebrates and represent the majority of the OR gene repertoire in mouse. While all Class I OR genes are segregated in a single cluster on chromosome 7, class II OR genes are located in clusters on all chromosomes except 12 and Y. The functional relevance of the sequence divergence observed between these two classes of receptors is still unclear. However, it has been proposed that Class I and II receptors bind volatile odorants that have low and high levels of hydrophobicity, respectively.

The gene structure and chromosomal arrangements of OR gene clusters observed in mouse is conserved in humans with an OR gene repertoire consisting of approximately 950 ORs [2]. While this total number may not seem that different from the number of OR genes present in the mouse genome, it is estimated that ~60–70% of these genes could be pseudogenes. Hence, humans may express approximately 300–350 functional ORs, three times less than are expressed in mice. The pseudogenization of the OR repertoire appears to parallel the evolution tree. The highest percentages of OR pseudogenes are observed in the human (~63%) and old-world monkey (~30%) genomes, while New World monkeys have a similar fraction of pseudogenes as found in the mouse genome (~20%). The increase in pseudogenes observed in humans, as well as in old-world primates, is likely the result of decreased selective pressure for olfactory function throughout evolution.

Vomeronasal Receptors (VRs)

The ►accessory olfactory system plays a critical role in the detection of and responsiveness to pheromones. Vomeronasal sensory neurons located in the ►vomeronasal organ express members of the Vomeronasal Receptor (VRs) superfamily that are putative pheromone receptors. These receptors are seven transmembrane GPCRs that are distinct from the OR superfamily. Two large families of VRs have been identified, V1R and V2R. In mouse, the V1R and V2R families are respectively comprised of ~200 and ~60 putative functional genes that are dispersed across several chromosomes [1,3]. While V1Rs, as ORs, are encoded by a single exon, the V2R gene structure is more complex and contains several coding exons. This difference in gene structure is also reflected in the overall V2R protein structure. In addition to features common to ORs and V1Rs, such as the seven

transmembrane domains, V2Rs contain a large extracellular N-terminal domain that binds ligands.

In humans, the majority (95%) of V1R sequences identified are pseudogenes. Five V1R genes that are predicted to encode functional receptors have been described, with at least one of them observed at the mRNA level in human olfactory mucosa [4]. Moreover, no intact V2R genes have been reported in humans. The high occurrence of VR pseudogenes in humans, as well as in primates, suggests that pheromone detection in these species is either not prevalent or mediated through other families of receptors.

Trace Amine-Associated Receptors (TAARs)

In addition to ORs, a second class of chemosensory receptors has been identified in the OE of mice. TAARs can recognize volatile amines and at least one of them is activated by urine from sexually mature male mice [5]. These observations suggest that TAARs may be implicated in the detection of social cues in mice. The mouse genome contains 16 TAAR genes, including 1 pseudogene, that are all located in a compact region of chromosome 10 and that share high sequence identities [6]. Of these 16 genes, 8 have so far been shown to be expressed in the OE. The coding region of TAAR genes consists of a single exon, which gives rise to proteins of approximately 350 amino acids that contain seven hydrophobic stretches of amino acids and conserved extracellular cysteine residues. In humans, 9 TAAR genes have been identified, including 3 pseudogenes [6]. It remains to be determined whether they are expressed in the human olfactory mucosa.

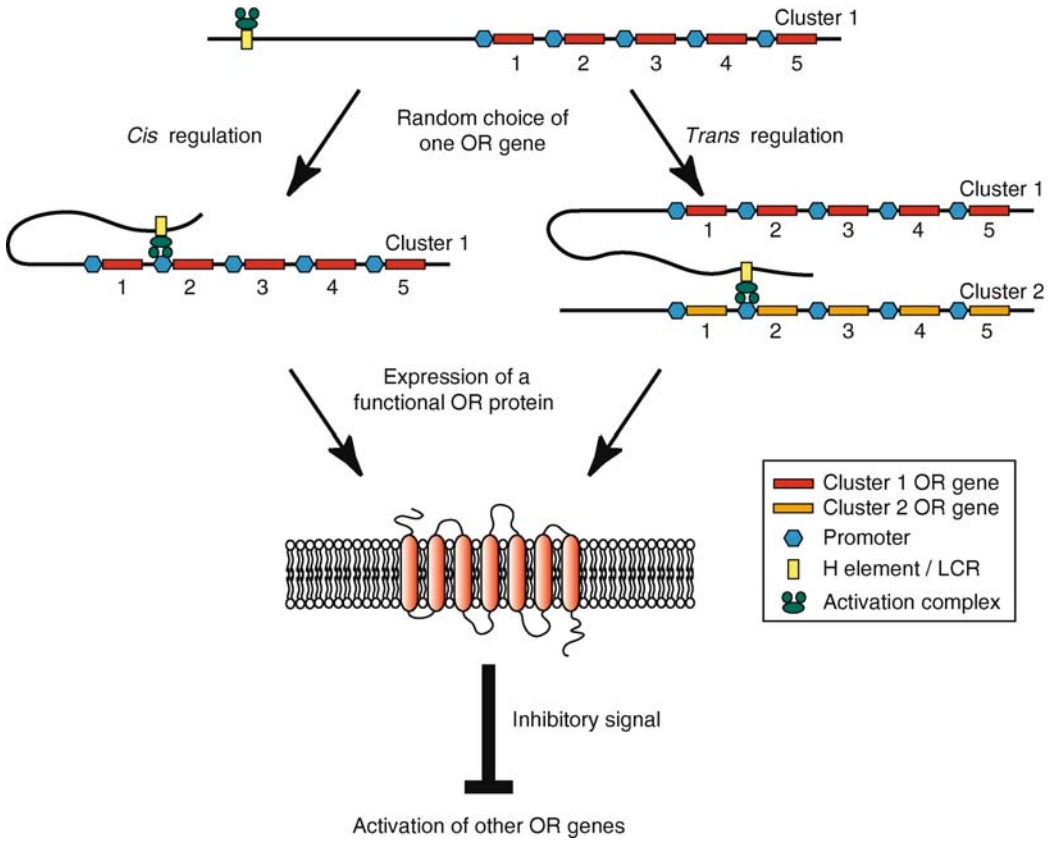
Regulation of odorant receptor gene expression

The development of a functional olfactory system is dependent on the tight regulation of OR gene expression in olfactory sensory neurons. Each OR is expressed in a small subset of neurons that are distributed in one of four defined but partially overlapping expression domains within the OE. Within each of these domains, neurons expressing the same OR are randomly distributed and each neuron expresses a single OR gene from the large repertoire available. Furthermore, a functional OR is expressed from only one of two gene ►alleles in a process termed ►monoallelic exclusion. The expression of a single OR per neuron is critical to define the profile of odorants recognized by this neuron. In addition, expression of the OR has also been shown to play a role in the accurate elaboration of ►topographic connections in the ►olfactory bulb. Mechanisms must therefore exist to first determine which subgroup of ORs will be expressed in a neuron based on its location in the OE. This is followed by the stochastic expression of a single receptor and by inhibition of expression of other OR genes in the same neuron. The mechanisms underlying these two levels of regulation of OR gene expression are beginning to be unraveled.

The spatial regulation of OR genes in neurons of the OE may be achieved through the combinatorial expression of various families of transcription factors in different regions of the OE. For some class II OR genes, the presence of short sequences upstream of the transcriptional start sites have been shown to be sufficient to induce appropriate spatial expression of these ORs in the OE. These short sequences contain regions recognized by homeodomain-containing transcription factors and by Olf1/EBF (O/E) family transcription factors. The LIM-homeodomain protein, Lhx2, can bind to the promoter region of at least one OR gene and is required for expression of class II OR genes [7]. Three members of the O/E family, O/E-1 to 3, are expressed in developing olfactory sensory neurons and the presence of O/E binding sequences in several OR gene promoter regions suggests they may also control OR gene expression [8]. However, the overlapping expression of these three family members in olfactory sensory neurons has made it difficult to establish their requirement for OR gene expression using gene-targeting approaches in mice.

The stochastic selection of expression of a single OR in a neuron is first dependent on the positive activation of gene expression through a *cis* or *trans*-acting mechanism (Fig. 2). It has been proposed that a region of homology upstream of each OR gene cluster, termed H, can act as a ►locus control region (LCR) to regulate expression of these genes in *cis* [9]. A similar mechanism is used to regulate the expression of photopigment genes in the visual system. This LCR would recruit proteins to form an activation complex that can randomly promote transcription of a single gene within the locus following chromatin rearrangements. Such a regulatory sequence has been identified far upstream of the mouse MOR28 gene cluster. Alternatively, a single H region could also regulate expression of OR genes in *trans* through interchromosomal interactions. In support of this hypothesis, the H region found upstream of the MOR28 gene cluster has been shown to interact with the promoter of several OR genes located on different chromosomes [10]. However, while deletion of H from the mouse genome affects expression of OR genes proximal to the location of H, the expression of OR genes outside of this gene cluster is unaffected [11,12].

Since only one allele of an OR gene is expressed in a single neuron, a mechanism must also exist to prevent transcription of the other allele as well as to prevent expression of other OR genes in the neuron. This may be achieved through a negative feedback mechanism in OSNs [9]. Expression of a full-length mRNA giving rise to a functional OR protein



Odorant Receptor: Genomics. Figure 2 Regulation of odorant receptor gene expression. Odorant receptor (OR) genes are arranged in clusters located on almost all chromosomes. A single OR gene is expressed per neuron through positive and negative mechanisms of regulation. An activation complex is recruited to a locus control region (LCR), termed H, located upstream of an OR gene cluster. Through chromosomal remodeling, this activation complex interacts in either *cis* or *trans* with a single OR gene promoter within a gene cluster to induce gene expression. This stochastic expression of a single OR protein leads to the generation of an unidentified signal that inhibits activation of other OR genes in the neuron by a negative feedback mechanism.

prevents the secondary activation of other OR genes. In contrast, expression of a full-length mRNA containing a premature stop codon from a pseudogene does not prevent activation of another OR gene. These observations suggest that expression of a functional OR protein leads to an as yet unidentified inhibitory signal that negatively regulates expression of other OR genes. In addition, the OR coding region contains regulatory elements importent to suppress expression of additional receptors [13]. Taken together, these mechanisms do not only prevent expression... Such a mechanism does not only prevent expression of two types of receptors in a single neuron but also serves to avoid the generation of receptorless neurons. The control of VR, and possibly TAAR, gene expression also ensures that a single receptor is expressed per neuron generated. Whether regulation of these families of genes is under the control of similar mechanisms to the ones identified for OR genes remains to be determined.

References

1. Zhang X, Zhang X, Firestein S (2007) Comparative genomics of odorant and pheromone receptor genes in rodents. Genomics 89:441–450
2. Glusman G, Yanai I, Rubin I, Lancet D (2001) The complete human olfactory subgenome. Genome Res 11:685–702
3. Yang H, Shi P, Zhang Y, Zhang J (2005) Composition and evolution of the V2r vomeronasal receptor gene repertoire in mice and rats. Genomics 86:306–315
4. Rodriguez I, Mombaerts P (2002) Novel human vomeronasal receptor-like genes reveal species-specific families. Curr Biol 12:R409–R411
5. Liberles SD, Buck LB (2006) A second class of chemosensory receptors in the olfactory epithelium. Nature 442:645–650
6. Lindemann L, Ebeling M, Kratochwil NA, Bunzow JR, Grandy DK, Hoener MC (2005) Trace amine-associated receptors form structurally and functionally distinct subfamilies of novel G protein-coupled receptors. Genomics 85:372–385

7. Hirota J, Omura M, Mombaerts P (2007) Differential impact of Lhx2 deficiency on expression of class I and class II odorant receptor genes in mouse. Mol Cell Neurosci 34:679–688
8. Michaloski JS, Galante PAF, Malnic B (2006) Identification of potential regulatory motifs in odorant receptor genes by analysis of promoter sequences. Genome Res 16:1091–1098
9. Serizawa S, Miyamichi K, Sakano H (2004) One neuron-one receptor rule in the mouse olfactory system. Trends Genet 20:648–653
10. Lomvardas S, Barnea G, Pisapia DJ, Mendelsohn M, Kirkland J, Axel R (2006) Interchromosomal interactions and olfactory receptor choice. Cell 126:403–413
11. Fuss SH, Omura M, Mombaerts P (2007) Local and as effect of the H element on expression of odorant receptor genes in mouse Cell 130:373–384
12. Nishizumi H, Kamasaka K, Inoue N, Nakashima A, Sakano H (2007) Deletion of the core-H region in mice abolishes the expression of three proximal odorant receptor genes in as, Proc Natl Acad Sci USA 104:20067–20072
13. Nguyen MQ, Zhou Z, Marks CA, Ryba NJP, Belluscio L, (2007) Prominent roles for odorant receptor coding sequences in allelic exclusion. Cell 131:1009–1017

Odorant Receptor Protein

Definition

►Odorant Binding Proteins.

►Odorant Receptor
►Odorant Receptor: Genomics

Odorants

►Olfactory Information

Odors

►Olfactory Information

Odotopic Representation

Definition

Odotopic representations involve a unique spatial pattern of activity in the olfactory system (e.g. a unique pattern of activated olfactory glomeruli) for odorant stimuli that evoke unique odor perceptions.

►Glomerular Map

Off Center Cells

Definition

►Visual Cortical and Subcortical Receptive Fields

Ohm's Law

Definition

The electrical current (I, in Amperes) that flows through an electrical resistor equals the potential difference (voltage, V, in Volts) across the resistor divided by the resistor's electrical resistance (Ohm, in Ω): $I = V/\Omega$.

►Action Potential
►Membrane Potential: Basics

Old/new Recognition

►Recognition Memory

Olfaction

Definition

The sense of smell. The process whereby odorant molecules bind to receptors in the olfactory epithelium

and leading to the generation and propagation of neural signals responsible for odor perception.

►Odor
►Odorant
►Odorant Receptor Neuron
►Odor Perception
►Olfactory Epithelium
►Olfactory Sense

Olfaction and Gustation Aging

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Synonyms

Senescence; Gerontology; Elderliness

Definition

Elderly adults often have an impaired ability to detect and recognize ►tastes and ►odors. Olfactory and gustatory impairment can be particularly harmful in aged individuals, given the likely contribution of such dysfunction to poor appetite, lower dietary energy and nutrient intakes, and the consumption of inappropriate food choices such as spoiled food. These phenomena may in turn influence body composition, nutritional stores, immune function, and disease status. Olfactory dysfunction can also be dangerous as it may prevent the detection of smoke or natural gas odors during household emergencies. Although the precise mechanisms underlying age-related changes in taste and smell remain uncertain, physiological changes associated with the aging process itself, diseases, medication usage, trauma, and environmental factors are all possible contributors. Flavor enhancement, increased dietary variety, and other interventions have been identified that can improve food intake and enhance eating enjoyment. Given the projected increases in the size and longevity of the elderly population in the U.S. and worldwide, additional effective interventions that can maintain or improve chemosensory function in this vulnerable population are needed.

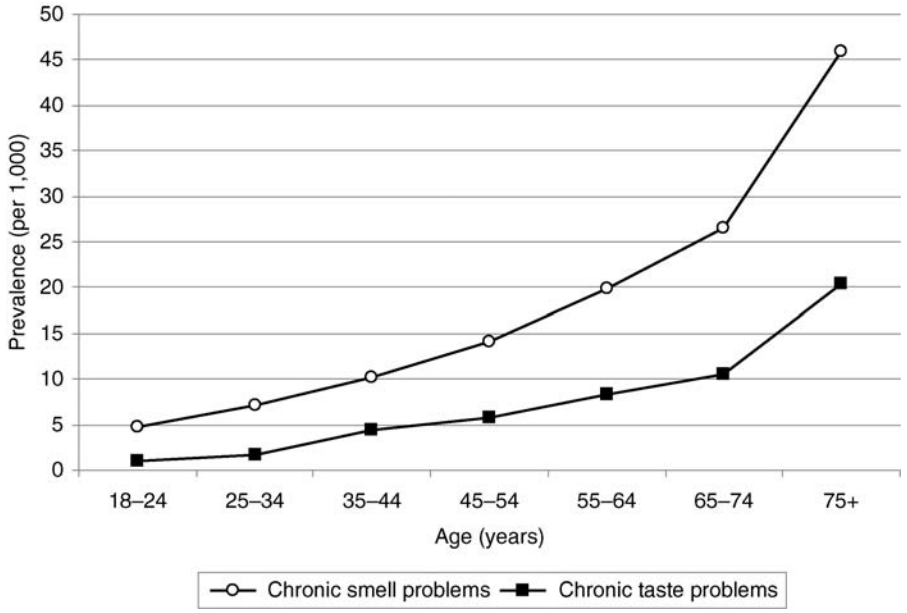
Characteristics

Introduction

It is generally accepted that all sensory modalities, including ►gustation, olfaction [see ►olfactory senses], vision [see ►binocular vision], audition [see ►auditory system], and somatosensation [see ►somatic sense] commonly decline with increasing age. Vision and auditory losses are perhaps most typically associated with the aging process, and these impairments are indeed highly prevalent among elderly adults, with approximately 34% of adults aged 65 years and older reporting vision and/or hearing impairment [1]. Taste and smell dysfunctions are also recognized as a common characteristic of old age, but frequently receive less attention, perhaps because their impact on mortality, morbidity, and functional status is less direct. Figure 1 illustrates the nearly exponential increase in self-reported taste and/or smell dysfunction with increasing age in a representative cohort of U.S. adults [2]. These data indicate that individuals aged 65+ years account for almost half (~41%) of the total number of individuals reporting chronic chemosensory problems. The prevalence of impairment is likely even higher when considering that self-reported data may underestimate the level of actual impairment as measured by objective testing.

The basic anatomy and neurobiology of the gustatory and olfactory systems have been fully described elsewhere [see taste, odor]. Briefly, taste signals are received by receptor cells located in ►taste buds in the ►gustatory papillae of the tongue and other structures of the oral cavity. Taste information is then transmitted to the ►gustatory cortex, orbitofrontal cortex [see ►cortex – orbitofrontal], ►amygdala, and lateral ►hypothalamus of the ►brain. Smell sensations are received by a small area of ►olfactory epithelial tissue located on the dorsal surface of the nasal cavity [see ►nasal passages], where odorants bind to receptors in olfactory neurons, which then transmit information about the identity and concentration of the chemical signal to the ►olfactory cortex in the brain.

Aging can influence different aspects of gustatory and olfactory sensory perception and sensitivity. Older individuals often require higher concentrations of an odorant or tastant to be present before detection and recognition of the chemical stimulus can be achieved. In other words, the detection and recognition ►thresholds for various tastes and smells are higher in older adults compared to younger. The magnitude of these changes can also vary across specific sensory qualities; salt taste [see ►taste – salt] thresholds appear to increase more during the aging process than sweet [see ►taste – sweet] thresholds. In addition, older individuals may have alterations in the ►suprathreshold perception of tastes and smells, such that more concentrated chemical stimuli are not perceived as more intense. Odor identification is also frequently poor among the elderly, although this may be due to both sensory impairment as well as cognitive and memory dysfunction resulting in difficulty with odor-naming tasks. In general, olfactory dysfunction is more common



Olfaction and Gustation Aging. Figure 1 Age specific prevalence rates (per 1,000) of self-reported chronic (≥3 months duration) chemosensory problems among individuals living in 42,000 randomly selected U.S. households (1994 Disability Supplement to the National Health Interview Survey). Adapted from Hoffman et al. [2] with permission © 1998 New York Academy of Sciences.

than taste dysfunction among the elderly population and individuals who describe problems with their sense of "taste" typically exhibit olfactory and not gustatory dysfunction, since it is difficult to distinguish true taste from ►retronasal olfaction [3]; strictly defined changes in taste alone are rare. Olfactory perception, however, declines with increasing age even in generally healthy men and women. As shown below, smell and taste changes associated with aging can manifest along a continuum of sensitivity, and can range from the total absence of sensation (e.g. ►ageusia) to a diminished or distorted sensation (e.g. ►hypogeusia, ►dysgeusia).

Terminology

Gustation	
Normogeusic	Normal taste sensory function
Hypogeusia	Diminished sensitivity of taste
Dysgeusia	Distortion of normal taste
Ageusia	Absence of taste
Olfaction	
Normosmic	Normal smell sensory function
Hyposmia	Diminished sensitivity of smell
Dysosmia	Distortion of normal smell
Parosmia	Distortion of odor perceptions when odor is present
Phantosmia	Odor sensations in absence of odor stimulus (i.e. olfactory hallucination)
Anosmia	Absence of smell
Cacosmia	Feeling ill in response to odors

Etiology

The causes of taste and smell dysfunction among elderly individuals are not completely understood. The olfactory epithelium is particularly vulnerable to age-associated dysfunction because of its anatomical location and proximity to environmental trauma, as well as a greater susceptibility to decreased ►neurogenesis secondary to its relatively small size (1–2 cm^2) and thinness. Declines in taste sensitivity were thought historically to result from a loss of functional taste buds over time, but more recent work indicates that taste bud numbers do not decrease with age and thus declines may be due to changes in taste cell membrane ion channels and receptors. The etiology of age-associated chemosensory dysfunction is further complicated by the varied environmental and medical factors that can also influence these systems and which frequently impact the elderly. Several possible causal factors are briefly described below:

Normal aging. One hypothesis for the decline in taste sensitivity with age is reduced taste receptor cell turnover rate, resulting in alterations in taste bud structure and subsequent dysfunction in older subjects. In addition, the olfactory mucosa may be gradually replaced by respiratory epithelium during the normal aging process, reducing smell perception and sensitivity. Animal data suggests that menopause may be associated with changes in olfactory perception, potentially contributing to further alterations in olfactory function among older women.

Diseases/infection. Acute or chronic nasal and sinus problems can lead to olfactory dysfunction by obstruction of the nasal passage, by viral-mediated damage to the olfactory receptors, and by altering the amount or composition of the mucus layer that odorants must traverse to reach the olfactory epithelial surface [3]. Neurodegenerative diseases such as ►Alzheimer's and ►Parkinson's disease have been associated with olfactory deficits. Recent work indicates that difficulty in odor identification predicts the transition from normal to mildly impaired cognition [4], and from mildly impaired cognition to Alzheimer's disease, suggesting that tests of olfactory perception may be useful in identifying apparently healthy and cognitively intact individuals who are at increased risk of developing severe cognitive impairment. Other representative diseases associated with impaired olfaction and gustation are listed below.

Medical conditions associated with taste or smell dysfunction

Neurological
- Alzheimer's disease
- Bell's palsy
- Damage to the chorda tympani
- Down's syndrome
- Epilepsy
- Familial dysautonomia
- Guillain-Barré syndrome
- Head trauma
- Korsakoff's syndrome
- Multiple sclerosis
- Parkinson's disease
- Raeder's paratrigeminal syndrome
- Tumors and lesions

Nutritional
- Cancer
- Chronic renal failure
- Liver disease including cirrhosis
- Niacin deficiency
- Thermal burn
- Vitamin B_{12} deficiency
- Zinc deficiency

Endocrine
- Adrenal cortical insufficiency
- Congenital adrenal hyperplasia
- Cretinism
- Cushing's syndrome
- Diabetes mellitus
- Hypothyroidism
- Kallmann's syndrome
- Panhypopituitarism
- Pseudohypoparathyroidism
- Turner's syndrome (gonadal dysgenesis)

Local
- Allergic rhinitis, atopy, and bronchial asthma
- Glossitis and other oral disorders
- Leprosy
- Oral aspects of Crohn's disease
- Radiation therapy
- Sinusitis and polyposis
- Xerostomic conditions including Sjögren's syndrome

Viral infections
- Acute viral hepatitis
- HIV infections
- Influenza-like infections

Other
- Amyloidosis and sarcoidosis
- Cystic fibrosis
- High altitude
- Hypertension
- Laryngectomy
- Psychiatric disorders

Adapted from Schiffman et al. [5] with permission © 2004 Humana Press Inc.

Medication usage. Taste alterations can be a common side effect of many medications. Medications typically do not produce total taste losses, but may produce metallic or bitter dysgeusias. Certain medications can be absorbed and then excreted in the saliva, where they can stimulate an adverse taste sensation or alter normal taste signal transduction. Other medications can diminish salivary output, decreasing the ability of tastant molecules to be dissolved and carried to the taste buds, or alter the composition of the olfactory mucus layer, modifying the absorption of odorants [6]. More than 250 medications are thought to interfere with smell and taste acuity, with selected medications listed below.

Medications associated with taste or smell dysfunction

Antianxiety agents
- Alprazolam (Xanax)
- Buspirone (BuSpar)

Antibiotics
- Ampicillin
- Azithromycin (Zithromax)
- Ciprofloxacin (Cipro)
- Clarithromycin (Biaxin)
- Enalapril (Vaseretic)
- Griseofulvin (Grisactin)
- Metronidazole (Flagyl)
- Ofloxacin (Floxin)
- Terbinafine (Lamisil)
- Tetracycline
- Ticarcillin (Timentin)

►Anticonvulsants
- Carbamazepine (Tegretol)
- Phenytoin (Dilantin)

►Antidepressants
- Amitriptyline (Elavil)

- Clomipramine (Anafranil)
- Desipramine (Norpramin)
- Doxepin (Sinequan)
- Imipramine (Tofranil)
- Nortriptyline (Pamelor)

Antihistamines and decongestants
- Chlorpheniramine
- Loratadine (Claritin)
- Pseudoephedrine

Antihypertensives and cardiac medications
- Acetazolamide (Diamox)
- Amiloride (Midamor)
- Amiodarone (Pacerone, Cordarone)
- Betaxolol (Betoptic)
- Captopril (Capoten)
- Diltiazem (Cardizem)
- Enalapril (Lexxel, Vasotec, Vaseretic)
- Hydrochlorothiazide (Esidrix)
- Nifedipine (Procardia)
- Nitroglycerin
- Propafenone (Rythmol)
- Propranolol (Inderal)
- Spironolactone (Aldactone)
- Tocainide (Tonocard)

Anti-inflammatory agents
- Auranofin (Ridaura)
- Beclomethasone (Beclovent, Beconase)
- Budesonide (Rhinocort)
- Colchicine
- Dexamethasone (Decadron)
- Flunisolide (Nasalide, AeroBid)
- Fluticasone (Flonase)
- Gold (Myochrysine)
- Hydrocortisone
- Penicillamine (Cuprimine)

Antimanic drugs
- Lithium

Antimigraine agents
- Dihydroergotamine (Migranal)
- Naratriptan (Amerge)
- Rizatriptan (Maxalt)
- Sumatriptan (Imitrex)

Antineoplastics
- Cisplatin (Platinol)
- Doxorubicin (Adriamycin)
- Levamisole (Ergamisol)
- Methotrexate (Rheumatrex)
- Vincristine (Oncovin)

Antiparkinsonian agents
- Levodopa (Larodopa; with carbidopa: Sinemet)

►Antipsychotics
- Clozapine (Clozaril)
- Trifluoperazine (Stelazine)

Antithyroid agents
- Methimazole (Tapazole)
- Propylthiouracil

Antiviral agents
- Ganciclovir (Cytovene)
- Interferon (Roferon-A)
- Zalcitabine (HIVID)

Bronchodilators
- Bitolterol (Tornalate)
- Pirbuterol (Maxair)

Lipid-lowering agents
- Atorvastatin (Lipitor)
- Fluvastatin (Lescol)
- Lovastatin (Mevacor)
- Pravastatin (Pravachol)

Muscle relaxants
- Baclofen (Lioresal)
- Dantrolene (Dantrium)

Pancreatic enzyme preparations
- Pancrelipase (Cotazym)

Smoking cessation aids
- Nicotine (Nicotrol)

Adapted from Doty and Bromley [7] with permission © 2004 Elsevier Inc.

Trauma/surgical interventions. Olfactory sensory information is transmitted by a single nerve (►cranial nerve I) which can be severed by a sharp upward blow to the nose (e.g. during an automobile accident or severe fall) proximal to the location where the nerve passes through the ethmoid bone. Gustatory sensation is transmitted via three cranial nerves (VII, IX, X) and thus is more resistant to trauma-induced dysfunction. In fact, even if one taste nerve is damaged or severed during surgery of the middle-ear region, the remaining nerves appear to compensate for the resultant loss of taste in that area of the mouth, thereby preserving overall taste perception [3].

Environmental factors. Olfactory neurons are the receptors for odorant chemical signals and therefore are directly exposed to potential airborne environmental toxins; taste receptors are specialized cells and thus the taste neurons are protected from this type of direct exposure. As a result, the olfactory system is vulnerable to damage from chemical fumes or metallurgical dust from occupational, industrial, household, or ambient sources. Tobacco smoke-induced hyposmia has also been documented.

Oral health and hygiene. Poorly fitting dentures or other dentition problems that impair chewing and mouth movements during eating can negatively impact retronasal olfaction by reducing the volatilization and movement of odor molecules from the oral cavity to the olfactory epithelium. Dentures may also cover the taste buds located in the soft palate in the roof of the mouth.

Consequences

Age-related losses of taste and smell perception can result in poor appetite, reduced energy and nutrient

intakes, and diminished eating enjoyment and motivation to eat. Consequently, chemosensory losses can lead to impaired nutritional status, reduced immune function, protein-energy malnutrition, involuntary weight loss, increased disease susceptibility or exacerbation of existing disease states, and overall decreased quality of life [6]. Poor taste and smell perception may lead to consumption of spoiled food and subsequently increased likelihood of food-borne illness. Taste and smell signals are important factors in meal initiation (via cephalic-phase stimulation of salivary, gastric, and pancreatic secretions; see ►food anticipatory behavior), continuation of food intake during a meal, and meal termination (via sensory-specific satiety). Taste and smell enhance enjoyment of meals and are the primary reinforcements of eating; maximal chemosensory acuity is thus especially important in elderly individuals for whom other sources of personal gratification may be infrequent.

The evidence for alterations of food intake as a result of olfactory or gustatory dysfunction alone is limited, however. Although chemosensory disturbances likely play an important role, other factors may also contribute to food intake dysregulation among older adults. Additional physiological factors, such as delayed gastric emptying and altered digestion-related hormone secretion and hormonal responsiveness, often act concurrently with chemosensory losses as well as with social, psychological, and medical factors to reduce food intake and promote weight loss in elderly adults.

Other consequences of taste and smell dysfunction include a decreased ability to detect natural gas leaks, volatile chemical fumes, and fires, which can result in increased risk for serious injury and death among elderly adults, their family members, and the general public. Elderly adults can have a heightened concern with personal hygiene and may overuse perfumes and colognes as a result of a lack of ability to detect offensive bodily or breath odors.

Therapeutic Strategies

While specific medical or pharmacological causes of olfactory and/or gustatory dysfunction can be resolved via appropriate treatment or pharmacotherapeutic modifications, chemosensory dysfunction that results from more intractable causes such as increasing age or environmental damage may be more resistant to improvement. In these cases, therapeutic strategies have been developed that improve food palatability and food intake, but do not alter impaired chemosensory pathways directly.

One intervention that is commonly employed is the use of flavor enhancements. Naturally-derived or chemically-synthesized concentrated odorants and flavorings can be added to individual foods to amplify or supplement the sensory signals provided by these foods. Flavor enhancement has been shown to increase the appeal of certain foods, attenuate decreases in energy intake, and improve immune status among elderly individuals [e.g. 8]. Many of these studies are limited by small sample sizes, short duration, and a lack of data regarding total dietary energy intake or nutritional status, and thus additional research is warranted. Olfactory declines tend to result in the predomination of ►bitter tastes, but this bitterness can be masked with salt, sweet, or flavored (e.g. coffee, chocolate) extracts. Other flavor enhancements such as spices, herbs, salt, or other compounds (e.g. monosodium glutamate, concentrated meat flavor, etc.) can improve food palatability and increase dietary intake. Recent media reports examining the increasing availability and marketing of spicy and highly flavored foods in U.S. groceries and restaurants attribute this national trend to an aging population and a resultant demand for spicier foods to overcome age-related sensory declines.

Another commonly employed strategy is to alter patterns of dietary variety in order to decrease sensory specific satiety and increase food intake. A recent study examined potential associations between low dietary variety and low body mass index (BMI) and dietary energy intake in older adults. In contrast to some but not all previous reports suggesting that dietary variety typically decreases with age, adults 61 years of age or older were shown to consume a greater total food variety compared with adults 60 years or younger [9]. However, older adults with low BMIs (<22 kg/m^2) consumed a lower variety of energy-dense foods and had a lower overall energy intake compared to older adults with higher BMIs [9]. Thus the results of this study suggest that consumption of a diet containing a high variety of energy dense foods may be associated with higher energy intake and greater body weight in older adults. Presentation of a variety of palatable foods with different textures, temperatures, and appearances can also promote increased intake even though the chemosensory characteristics of the foods are not altered. The order of foods eaten can also be rotated to stimulate intake and reduce sensory-specific satiety.

Zinc supplementation and hormone replacement therapy have been suggested as additional therapeutic methods for improving taste and smell function, respectively. Hormone replacement in healthy postmenopausal women does not appear to improve performance on olfactory detection, discrimination, or recognition tasks. A recent randomized, double-blind, placebo-controlled study examining zinc supplementation in older Europeans aged 70–87 years demonstrated that supplementation with 30 mg zinc per day resulted in increased salt taste acuity, but not sweet, sour, or bitter taste acuity, among subjects recruited in one of two geographical regions [10], suggesting the efficacy of this approach may be limited to individuals with poor

baseline zinc status or another trait common to those subjects examined in this region.

Audible and visual gas detection systems exist that will notify an individual of a natural gas leak; these systems are especially important for elderly individuals with olfactory losses who may be unable to detect the "rotten-egg" smell of mercaptan which is added to natural gas as a warning agent. Novel mechanisms for visually indicating the presence of food-borne pathogens, via sensors or temperature logs integrated within food packaging materials, are in development and may ultimately help older adults who cannot discriminate spoiled from wholesome food using taste or smell cues.

Conclusion

An awareness of changes in taste and smell in association with increased age has existed for thousands of years – the Roman statesman Cicero (106–43 BC) stated that "I am grateful to old age because it has made me less interested in good food and more interested in good conversation." Projected increases in both the size and average lifespan of the elderly population in the U.S. and worldwide will lead to an increased prevalence of chemosensory dysfunction, with a concomitant increase in the negative health consequences of these dysfunctions. Additional effective interventions that can maintain or improve chemosensory function in this vulnerable population are needed.

References

1. Lam BL, Lee DJ, Gómez-Marín O, Zheng DD, Caban AJ (2006) Concurrent visual and hearing impairment and risk of mortality. Arch Ophthalmol 124:95–101
2. Hoffman HJ, Ishii EK, Macturk RH (1998) Age-related changes in the prevalence of smell/taste problems among the United States adult population. Results of the 1994 Disability Supplement to the National Health Interview Survey (NHIS). Ann N Y Acad Sci 855:716–722
3. Duffy VB, Chapo AK (2006) Smell, taste, and somatosensation in the elderly. In: Chernoff R (ed) Geriatric nutrition: the health professional's handbook. Jones and Bartlett Publishers, Sudbury, MA, pp 115–162
4. Wilson RS, Schneider JA, Arnold SE, Tang Y, Boyle PA, Bennett DA (2007) Olfactory identification and incidence of mild cognitive impairment in older age. Arch Gen Psychiatry 64:802–808
5. Schiffman SS, Rogers MO, Zervakis J (2004) Loss of taste, smell, and other senses with age: effects of medication. In: Bales CW, Ritchie CS (eds) Handbook of clinical nutrition and aging. Humana Press Inc., Totowa, NJ, pp 211–289
6. Seiberling KA, Conley DB (2004) Aging and olfactory and taste function. Otolaryngol Clin N Am 37:1209–1228
7. Doty RL, Bromley SM (2004) Effects of drugs on olfaction and taste. Otolaryngol Clin N Am 37:1229–1254
8. Schiffman SS, Warwick ZS (1993) Effect of flavor enhancement of foods for the elderly on nutritional status: food intake, biochemical indices, and anthropometric measures. Physiol Behav 53:395–402
9. Roberts SB, Hajduk CL, Howarth NC, Russell R, McCrory MA (2005) Dietary variety predicts low body mass index and inadequate macronutrient and micronutrient intakes in community-dwelling older adults. J Gerontol A Biol Sci Med Sci 60A:613–621
10. Stewart-Knox BJ, Simpson EEA, Parr H et al (2008) Taste acuity in response to zinc supplementation in older Europeans. Br J Nutr Jul 99:129–136

Olfaction/Gustation Sensing Chemical Stimuli

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Introduction

The ►sensory systems are the devices with which we perceive the external world, while sensory perception amounts to the deconstruction of this external world for subsequent reconstruction of the internal representation. Animals indeed discriminate and recognize numbers of physical and chemical signals in their environment, which profoundly influence their behavior and provide them with essential information for survival [1].

A number of sophisticated sensory ►modalities available for that purpose all rely on a specific ►coding, that is a set of rules by which information is transposed from one form to another. For the ►chemical senses, this transposition concerns the ways by which chemical information give rise to specific neuronal responses in a dedicated sensory organ [2]. ►Olfaction is applied to chemosensory systems that detect chemicals emanating from a distant source. In contrast, when chemical senses require physical contact with the source for detection, they are called ►gustatory.

The origin of chemical detection (also called ►chemosensation) dates back to prokaryotes and has evolved into four distinct modalities in most vertebrates [3]. As we shall see below, the ►main olfactory system, the ►accessory olfactory system, the gustatory system and the so-called ►common chemical sense mostly carried by ►trigeminal sensory ►neurons, all differ with respect to receptor molecules, ►receptor cells and wiring of the receptor cells with the central nervous system (CNS).

Unlike most animals, humans primarily rely on ►vision and ►audition. The relevance of these two senses for human life have driven intense research into

the elucidation of visual and auditory perception, leaving the understanding of the more primitive chemical senses behind. Nevertheless, during the last two decades, modern neuroscience has made considerable progress in understanding how the brain perceives, discriminates, and recognizes ►odorant molecules. This growing knowledge took over when the chemical senses were no longer considered only as a matter for poetry or the perfumes industry [4]. Over the last decades, chemical senses captured the attention of scientists who started to investigate the different stages of chemosensory systems. Distinct fields such as genetic, biochemistry, cellular biology, neurophysiology and ethology have contributed to provide a picture of how chemical information is processed in the olfactory and gustatory systems as it moves from the periphery to higher areas of the brain. So far, the combination of these approaches has been most effective at the cellular level but there are already signs, and even greater hope, that the same is gradually happening at the systems level. ►Taste and olfaction researches caught up with the advance in other sensory systems through dramatic developments achieved in a recent past. All these advances started with the discovery of the genes encoding the chemosensory receptors of the olfactory [5] and taste [6] systems. Then, further achievements were performed following the development of new experimental tools brought into play by geneticists and molecular biologists and subsequently used by the physiologists.

Although far from being complete, to date we have a fairly comprehensive view about how chemicals interact with their cognate receptors to initiate signal ►transduction in the sensory receptor cells [7]. We know now how the sensory information is first transduced in the olfactory and gustatory systems by specialized ►receptor neurons located in dedicated sensory organs. Among the different relays along the olfactory and gustatory pathways, local circuits in the second- and third-order brain areas then process the simple mono-phasic sensory signal conveyed by the sensory neurons [8] to convert it into a multi-dimensional code, including among others a ►combinatorial coding. We are now about understanding how chemical information is encoded and processed, but it is the challenge for the next decade to uncover how sensory information triggers specific behavioral outputs.

Two Distinct Chemical Stimuli

According to the phylogenetic position of the species, a number of very different but sophisticated ways, based on distinct sensory channels, have risen in order to process information from the external world in subsequently reformatted internal states [8,9]. The following synopsis describes the contributions of our understanding of chemical sensory systems that encompasses two intermingled senses: olfaction and taste. For the sake of clarity, these two modalities are presented separately, although they act, most often, in a concerted manner that gives rise to the so-called ►flavor [10,11]. Although chemical perception of a food or a flower arises from the central integration of multiple sensory inputs, it is possible to distinguish the different modalities contributing to it, especially when attention is drawn to particular sensory characteristics. Nevertheless, our experiences of the flavor or a fragrance are simultaneously of an overall unitary perception [11]. Research aimed at understanding the mechanisms behind this integrated chemical perception is, for the most part, relatively recent. However, ►psychophysical, neuroimaging and neurophysiological studies on cross-modal sensory interactions involved in olfaction and taste perception have started to provide an understanding of the integrated activity of sensory systems that generate such unitary perceptions, and hence the mechanisms by which these signals are functionally united when anatomically separated. Below I present the emerging picture that originates from the recent researches on ►odor and taste. The current model of chemosensory information processing supposes a particular combination of sensory inputs, ►temporal and ►spatial concurrence, and ►memory functions [12].

The Sense of Smell

Mammalian olfactory system regulates a wide range of multiple and integrative functions such as physiological regulation, emotional responses (e.g., anxiety, fear, pleasure), reproductive functions (e.g., sexual and maternal behaviors) and social behaviors (►social chemosignals are involved in the recognition of conspecifics, family, clan or outsiders, for examples) [13]. To achieve this large variety of functions, two anatomically and functionally separate sensory organs are required. First, the ►vomeronasal organ is specialized to sense chemical compounds (e.g., ►pheromones), specific regarding the origin of the source. By transferring information through the ►accessory olfactory bulb, this sensory organ provides information about the social and sexual status of other individuals within the species. However, recent evidence also suggests some cross-talk between the main and accessory systems. Recent molecular and neurophysiological approaches have offered new insights into the mechanisms of pheromone detection in rodent and into the sensory coding of pheromone signals that lead to the gender discrimination or aggressive behavior, for example. They show that the vomeronasal organ does not have an exclusive function with regard to pheromone recognition but it responds also to molecules other than pheromones, at least in rodents. Thus, it is highly debated today, to what extent only the vomeronasal organ can detect

pheromones, and also to what extent it can only detect pheromones [14].

In mammals, the second sensory organ is represented by the ►olfactory epithelium, which recognizes more than a thousand airborne volatile molecules called odorant compounds (or odorants) [15]. This neuroepithelium is connected to the next central station for processing ►olfactory information: the main olfactory bulb (referred to below as the olfactory bulb). While advances in understanding olfactory transduction were taking place, interest in the olfactory bulb, was also intensified [15]. This growing interest has been spurred on by discovering the way the sensory organ connects to the olfactory bulb. Finally, several observations indicate that descending forebrain axons from various areas can selectively modulate olfactory bulb odorant-evoked responses. These data clearly show, at the very least, that olfaction processing does not involve simple feed-forward pathways. Rather, in real world situations where information has to be continually updated, olfactory responses that originate from the periphery are modulated by forebrain circuits and their projections to the olfactory bulb circuit.

Evolutionary Dimensions of Olfaction

The main olfactory system detects only volatile odorants, whereas the accessory system picks up less volatile or even water-soluble odorants. It is generally thought that the accessory system specializes in pheromone detection, whereas the main system detects common odorants [2]. In terrestrial environments, chemical signals can be either volatile or non-volatile. Accordingly, terrestrial vertebrates have two functionally and anatomically distinct olfactory systems: one detecting volatile cues (the main olfactory system) and another thought to process mostly non-volatile signals (the ►vomeronasal system). Such a dichotomy has been brought into play to support the long-standing hypothesis according to which the vomeronasal system evolved as an adaptation to terrestrial life. Today, accumulated evidence rather contests this assumption. The evolution of a vomeronasal system in aquatic species might rather provide a selective advantage for terrestrial life, and consequently it could have been retained in many species of terrestrial vertebrates. In spite of this, anatomical studies, and most recently molecular studies indicate that the selective pressure to retain vomeronasal chemosensory input has been lost in higher primates. As a result, Old World primates, apes and humans might not have retained a functional vomeronasal system. Alternatively, species without a distinct vomeronasal system may still have an accessory olfactory system intermingled within the main system. Thus, it is yet possible that the accessory system did not "arise" at some point of the vertebrate evolution, but rather it just became anatomically separated from the main system [16].

As our knowledge about the neurobiology of olfaction is growing, it is becoming incredibly evident that the main olfactory systems of animals in disparate phyla have many striking features in common. For instance, vertebrate and insect olfactory systems display common organizational and functional characteristics [17]. Further recent works that were undertaken to broaden this scope to include nematodes, mollusks and crustaceans have only strengthened this assumption. The initial common event, shared by all odorant detection systems, requires the specific interaction of odorant molecules with specific receptors expressed on the cilia of sensory olfactory neurons before conveying information to central structures [18]. Basically, four features are shared by all olfactory systems. They include: (i) the presence of ►odorant binding proteins [19] in the fluid overlying the receptor cell dendrite; (ii) the requirement of ►G-protein-coupled receptors (GPCRs) [20] as ►odorant receptors ([5,21]; even though some sensory neurons may use transmembrane guanylate cyclase receptors such as in *C. elegans* and mammals); (iii) the use of a two-step signaling cascade in odorant transduction; and (*iv*) the presence of functional structures at the first central target in the ►olfactory pathway. All these characteristics may represent adaptations that have evolved independently, and therefore might provide us with valuable information about the way the nervous system processes odorant stimuli. Alternatively, these shared properties may instead reflect underlying homology, or could have arisen independently due to similar constraints.

Similarly, the perception of odorant molecules arises from invariant series of information-processing steps that occur in anatomically distinct structures. In mammals, the olfactory epithelium contains several thousands of bipolar olfactory sensory neurons, each projecting to one of several modules in the olfactory bulb. These discrete and spherical structures, called ►olfactory glomeruli, are both morphological and functional units made of distinctive bundles of neuropil. This term reflects both the homogeneity of the sensory inputs conveyed by the ►olfactory nerve, and the degree to which the neurons in the same glomerular unit are interconnected. In different species, each glomerular structure results from the convergence in the olfactory bulb of 5–40,000 axon terminals of sensory neurons that express the same odorant receptor. As each group of glomerulus-specific output neurons is odorant receptor-specific, they form a morphologically defined network somewhat analogous to ►ocular-dominance columns in ►visual cortex or to ►barrels in the ►somatosensory cortex [22]. It is also worth noting that a number of mechanisms have evolved to ensure that only a single odorant receptor is expressed per sensory cell. In rodents, tight transcriptional control results in the choice of one among a possible thousand odorant receptor genes. This

extremely large repertoire of odorant receptors is undergoing rapid evolution, with at least 20% of the genes lost to frame-shift mutations, deletions and point mutations that are the hallmarks of ►pseudogenes [3,4]. Facing a changing environment, this characteristic may reflect the pressure made on a gene family to diversify and generate large numbers of new receptors that might confer new selective advantages. Interestingly, approximately 50% of human odorant receptor genes carry one or more coding region disruptions and are therefore considered pseudogenes. This massive pseudogenization of the odorant receptors repertoire in humans and Old World primates is preceded by a moderately high level of pseudogenes (approximately 30%). Thus, there has been a decrease in the size of the intact odorant receptor repertoire in apes relative to other mammals, with a further deterioration of this repertoire in humans. Since such decline occurred concomitant with the evolution of full ►trichromatic vision in two separate primate lineages, it is possible that the weakening of olfaction results from the evolution of full ►color vision in our primate ancestors [23]. However, several overlooked human features such as the structure of the nasal cavity, retronasal smell, olfactory brain areas, and language call for reassessing the status of the sense of smell in human beings [24].

From Odorant Molecules to Cortical Centers

The olfactory system is responsible for correctly coding sensory information from thousands of odorous stimuli. To accomplish this, odor information has to be processed throughout distinct levels. At each one, a modified representation of the odor stimulus is generated. To understand the logic of olfactory information processing, one has first to appreciate the coding rules generated at each level, from the odorant receptors up to the level of the ►olfactory cortex [25,26]. In mammals, the initial event of odor detection takes place at a peripheral olfactory system, the olfactory epithelium of the nasal cavity. There, olfactory transduction starts with the activation of some of the thousand different types of odorant receptors located on the cilia of sensory neurons that comprise the olfactory neuroepithelium. The sensory neurons project to a small number of olfactory glomeruli paired on both the medial and lateral aspects of the olfactory bulb. About 20–50 second-order neurons emanate for each glomerulus and project to a number of higher centers, including the olfactory cortex. Using a trans-synaptic tracer expressed in olfactory receptor neurons under the control of two specific olfactory receptor promoters, it was possible to demonstrate that the projection of bulbar output neurons receiving sensory inputs from homologous glomeruli, form reliable discrete clusters in different regions of the olfactory cortex. Such clusters can be partly overlapping, but clearly distinct between odorants (a process called ►odor maps). A certain overlap between more diffuse projections to higher olfactory centers may constitute the anatomical basis for crosstalk between information strands emanating from different odorant receptors. This characteristic is probably helpful to integrate multiple modules of olfactory information into a composite ►gestalt, specific for a particular scent made of numerous chemical compounds.

From the External World of Odorants to Internal States

Even in humans, during the first hours of life in the open air, the newborn child behaves like a macrosmatic animal. Meanwhile, the human being is totally dominated by ►affect. During the rest of the development period and all of adult life, olfaction will remain the sense that opens the most direct route to the affective sphere [27].

To achieve this privileged relationship between olfaction and affect, the two olfactory systems connect different areas. The vomeronasal system mainly projects to the ►hypothalamus and ►amygdala that are known to control innate endocrine or behavioral responses. In contrast, in the main olfactory system, information is processed in cortical areas, which may give rise to the conscious representation of odorant molecules. In primates, the projections from the olfactory bulb reach medial olfactory areas including the ►piriform (►primary olfactory) ►cortex, ►entorhinal cortex, cortico-medial nucleus of the amygdala, and ►olfactory tubercle. From the ►piriform cortex (Primary olfactory cortex), projections reach ►area 13, a part of the caudal ►orbitofrontal cortex, and from there on to different orbitofrontal areas.

Odors are important in emotional processing; yet relatively little is known about the representation of the affective qualities of odors in the human brain. Recent results suggest that there is a ►hedonic map of the sense of smell in brain regions such as the orbitofrontal cortex [26,27]. These results have implications for understanding the psychiatric and related problems that follow damage to these brain areas. It is remarkable that amongst all the senses, olfaction possesses a particular link with the ►limbic system that was taken to be the "nose-brain" (the actual meaning of ►rhinencephalon). Today, it is clear that the primary olfactory cortex projects to the entorhinal area, which in turn projects to the ►hippocampus. Thus, we see reintroduced, after years of fervent affirmation followed by years of fervent denial, the idea that the hippocampus receives olfactory inputs. The pathway that links olfaction to the limbic system seems to be privileged. The path from the olfactory epithelium is more direct than the path from sensory surfaces such as the skin. Moreover, the primary olfactory cortex projects to the amygdala, in large part onto a particular cell group, the lateral nucleus

of the amygdala, by bypassing the neocortex. However, while it is clear that the olfactory bulb projects to the amygdala in rodents, one wonders whether such a connection is still present in humans. For instance, the vomeronasal organ and the corresponding region of the accessory ►olfactory bulb are thought to form an apparatus dedicated to the processing of sexually significant odors, but in the fully formed human body none of these structures has been identified.

Non-invasive functional imaging studies of the human olfactory system revealed that the sense of smell is organized similarly to other sensory modalities, and that the specific psychological characteristics of olfaction should be attributed to an early involvement of the limbic system rather than a conceptually different mode of processing. Taking into account the high connectivity of limbic structures and the fact that activation of the amygdala immediately induces ►emotions and facilitates the coding of memories, one should not be so surprised to uncover the special relationship that links olfaction with emotions and memory.

In sum, as a result of unprecedented developments in methods for examining the structure, function, and neurochemistry of olfactory system circuits, research in olfaction has progressed dramatically in recent years. Applying new technologies, including those of neurophysiology and functional imaging should help to unravel the mysteries of how chemical perception gives rise to unique olfactory experiences such as those triggered by the exquisite fragrance of jasmine.

The Sense of Taste

The ►gustatory sense enables animals to detect and discriminate among foods, to select nutritious diets, and to initiate, sustain and terminate ingestion for the purpose of maintaining energy balance [11]. For most mammals, the decision to ingest a particular food depends not only on its taste but also on its appearance, familiarity, odor, texture, temperature and, importantly, its post-ingestive effects (for example, the ability to reduce hunger). For humans, such factors also include cultural acceptance as well as the social, emotional and cognitive contexts under which a given food is eaten. Revealing the logic of the neural mechanism of gustation is currently a major topic in modern neurobiology, given the efforts made so far towards the understanding of how complex feeding behaviors can become dysfunctional (as in the case of anorexia or obesity) [28].

In marked contrast to the olfactory system, the gustatory system has little discriminative power. Sapid stimuli come as five basic tastes, sweet, umami, bitter, salty and sour while the olfactory sensory organ recognizes about 10,000 airborne volatile molecules, in human beings. Taste stimuli are detected by assemblies of about 100 cells that form well-known specialized morphological structures, the ►taste buds, which are located in the chemosensory papillae on the tongue. However, we know astonishingly little about the precise function of these small chemosensory organs. Their characterization has largely relied on cytological and ultrastructural data [29].

The Peripheral Gustatory System

Although the sense of taste is generally associated solely with the activation of taste buds, placing food or drinks in the mouth automatically elicit responses from several distinct systems that monitor the temperature, the sound when chewing, and texture of the food. In this regard, gustation is inherently multisensory [30]. Every gourmet worth his/her salt is aware that the list of the five basic tastes should also include further perceptual categories such as astringent, fatty, tartness, water, metallic, starchy, cooling, tingling and pungent. The subjective sensations associated with these non-primary tastes result from the co-activation of taste and specialized somatosensory neurons located in the oral cavity. These specialized neurons surround taste buds, and include different classes of mechano- and chemoreceptors that transmit information on the food's texture, weight and temperature to the brain mainly via the ►trigeminal system.

Transduction Pathways for Primary Tastes

In the oral chemosensory epithelia, taste buds contain about 50–100 ►taste receptor cells (TRCs) of various types. These TRCs are embedded in stratified epithelia and are distributed throughout the tongue, palate, epiglottis and esophagus. On their apical end, taste cells make contact with the oral cavity through a small opening in the epithelium called the taste pore, which is filled with microvilli. The plasma membranes of these microvilli contain many of the receptors responsible for detecting the presence of various tastants. Small clusters of TRCs are electrically and chemically coupled by ►gap junctions allowing their synchronous activation.

On the palate and the anterior tongue, TRCs are innervated by the ►chorda tympani nerve and greater superior petrosal branches of the ►facial nerve, respectively. These nerves transmit information about the identity and quantity of the chemical nature of the tastants. On the epiglottis, esophagus and posterior tongue, TRCs are innervated by the lingual branch of the ►glossopharyngeal nerve and the superior laryngeal branch of the ►vagus nerve. These nerves are responsive to tastants and participate primarily in the brainstem-based arch reflexes that mediate swallowing (ingestion) and gagging (rejection). TRCs transmit information to the peripheral nerves by releasing ►ATP to ►P2X purinergic receptors located on the postsynaptic membrane of primary afferents. Other transmitters

such as ►serotonin, ►glutamate and ►acetylcholine might also be released.

The key to understanding how TRCs transduce chemical stimuli lies in determining the identification and operation of different types of taste receptor and their downstream signaling pathways. As for olfaction, proteins belonging to the G-protein-coupled receptor superfamily have been established as the receptors for sweet tastants (taste receptor, type 1, member 2 (T1R2)/T1R3), amino acids (T1R1/T1R3) and bitter (T2Rs) tastants. The sensations associated with the other two primary tastants, sour and salt (NaCl), are mediated by ion channels of the ►transient receptor potential (TRP) and ►epithelium sodium channel (ENaC) superfamilies, respectively.

Taste Pathway

Receptor cell depolarization leads to the release of neurotransmitter, which generates first post-synaptic potentials and then action potentials in the associated nerve endings. The axons, whose cell bodies lie in the sensory ganglia of the cranial nerve, enter the medulla and synapse in the region of the ►nucleus of the solitary tract (N. tractus solitarii). The nerve cells in this part of the medulla are important in mediating salivation and other gastrointestinal reflexes. Their axons also cross over, and relay via the contralateral ►medial lemniscus, to the ►thalamus, and thence to the post-central gyrus in the region of the ►insula.

Coding in the Periphery

Two schemes have been proposed to explain how taste processing is achieved through the interaction of TRCs with their associated afferent nerve fibers: the ►"labeled line" model and the "►across-fiber pattern" (or "distributed") model [11]. The assessment of experimental data supporting either of these hypotheses constitutes an important source of debate in the field of gustatory physiology. The ►labeled line hypothesis (model) implies that sensory information is processed through segregated and feed-forward circuitry that connects peripheral sensory receptors to higher-order structures in the CNS. By contrast, across-fiber pattern models propose that sensory fibers (or neurons) are broadly tuned, in such a way that stimulus identity and intensity are specified by a unique combinatorial pattern of activity distributed across populations of neurons.

At the peripheral level one can find experimental support for both labeled line and across-fiber pattern models, but recent data from genetic studies strongly favor the existence of labeled lines. The validity of either model at the periphery should not necessarily be generalized to CNS circuits. In contrast to the periphery, the CNS possesses the anatomical structure required for ►multisensory integration and this ability might determine a difference in coding strategies between the CNS and peripheral nervous system (PNS). In fact, much of the current neurophysiological data describe gustatory processing as multisensory and distributed across several brain regions [31].

In contrast to the highly specialized information transfers performed by TRCs and peripheral fibers, central gustatory processing seems to be distributed, probably as a result of its capacity for ►multimodal (multisensory) integration. Approaching the encoding of a gustatory stimulus in this manner will provide new insights into how information is encoded, beyond the theories that have been historically proposed to model the mechanisms by which taste quality is coded in the periphery. Indeed, how these sensory modalities are synthesized into a single percept, which allows animals to rapidly decide whether to ingest or reject a particular food, is the greatest challenge for the near future in gustatory physiology.

The growth of our knowledge in gustation has not yet reached the level of olfaction. Many fundamental problems in the emerging field of taste are still to be resolved. For example, what is the coding logic for multisensory integration? How is a taste percept generated from activation of labeled- or distributed-lines? Answers to these basic questions might help us understand how the brain makes sense of chemical compounds that we daily place in the mouth.

Concluding Remarks

Smell and taste problems can have a big impact on our lives. Because these senses contribute substantially to our enjoyment of life, our desire to eat, and be social, smell and taste disorders can be serious. When smell and taste are impaired, we eat poorly, socialize less, and as a result, feel worse. Many older people experience this problem. But not only chemical signaling make us happier, smell and taste also warn us about dangers, such as fire, poisonous fumes, and spoiled food. Certain jobs require that these senses be accurate – chefs and firemen rely on taste and smell. Loss or reduction of the sense of smell (►anosmia or ►hyposmia) may be due to damage to the olfactory mucosa (e.g., in smoking) or to the olfactory bulbs or tracts. CNS disorders (e.g., some types of ►epileptic seizures) can cause ►parosmia (disturbed sense of smell). Like olfaction, the sense of taste is important in regulating appetite and to some degree, dietary intake. Loss or reduction of the ability to taste is termed ►ageusia or ►hypogeusia and is a widely distributed feature of ageing as more than 200,000 people visit a doctor with smell and taste disorders every years in the United States.

Strikingly, olfactory and gustatory systems are endowed with rejuvenating properties throughout life. Olfactory and taste cells are one of the few cell types of the nervous system to be continuously replaced when the sensory organs become old or damaged. Scientists are examining this phenomenon,

called adult ►neurogenesis [32], while studying ways to use this potential to replace other damaged nerve cells of the CNS.

Smell and taste have here been presented separately but one should keep in mind that about 75% of what we perceive as taste actually comes from smell. It is the odor molecules from food that give us most of our taste sensation as taste buds allow us to perceive only five flavors. Of all our senses, smell is our most primal. Animals need the sense of smell to survive. Although a blind rat might survive, a rat without its sense of smell can't mate or find food. For humans, the sense of smell communicates many of the pleasures in life–the aroma of a pot roast in the oven, fresh-cut hay, a rose garden. Although our sense of smell is our most primal, it is also very complex. To identify the smell of a rose, the brain analyzes simultaneously over 300 odor molecules. The aroma of a baking apple pie sends one message when someone is hungry and quite another when that person has just finished a six-course meal!

Although recent discoveries in the field of molecular biology raise the hope of a future understanding of the transduction and peripheral coding of odors and tastes, it seems that they imply a risk: to make us forget that in the other extreme of knowledge, that of maximal complexity, the evolution of cognitive sciences allows an epistemologically fruitful reformulation of information-processing problems. In the future, we have to try to find out to what extent higher-order processes interact with the sensory level in order to produce sufficiently reliable representations, as compared with what we know about vision and audition, for instance. After all, we should not forget what Sigmund Freud, addressing the members of the Vienna Psycho-analytical Society, said about olfaction: "*the organic sublimation of the sense of smell is a factor of civilization*."

References

1. Finger T, Simon SA (2002) The Cell Biology of Lingual Epithelia. In: Finger T, Silver WL, Restrepo D (eds) The neurobiology of taste and smell. Vol 2. Wiley-Liss, New York, 12: 287–314
2. Ache BW (1991) Phylogeny of smell and taste. In: Getchell TV, Bartoshuk LM, Doty RL, Snow JB (eds) Smell and taste in health and disease. Raven, New York pp 3–18
3. Mombaerts P (2004) Genes and ligands for odorant, vomeronasal and taste receptors. Nat Rev Neurosci 5:263–278
4. Mombaerts P (2004) Love at first smell – the 2004 Nobel Prize in physiology or medicine. N Engl J Med 351:2579–2580
5. Buck L, Axel R (1991) A novel multigene family may encode odorant receptors: a molecular basis for odor recognition. Cell 65:175–187
6. Margolskee RF (2005) Sensory systems: taste perception. Sci STKE 290:tr20
7. Ache BW (1994) Towards a common strategy for transducing olfactory information. Semin Cell Biol 5:55–63
8. Dalton P, Doolittle N, Nagata H, Breslin PAS (2000) The merging of the senses: integration of subthreshold taste and smell. Nat Neurosci 3:431–432
9. Olender T, Feldmesser E, Atarot T, Eisenstein M, Lancet D (2004) The olfactory receptor universe – from whole genome analysis to structure and evolution. Genet Mol Res 3:545–553
10. Smith DV, St. John SJ (1999) Neural coding of gustatory information. Curr Opin Neurobiol 9:427–435
11. Simon SA, de Araujo IE, Gutierrez R, Nicolelis MAL (2006) The neural mechanisms of gustation: a distributed processing code. Nat Rev Neurosci 7:890–901
12. Algom D, Cain WS (1991) Chemosensory representation in perception and memory. In: Bolanowski SJ, Gescheider GA (eds) Ratio scaling of psychological magnitude. Hillsdale. Lawrence Erlbaum Associates, N.J., pp 183–198
13. Dulac C, Torello AT (2003) Molecular detection of pheromone signals in mammals: from genes to behaviour. Nat Rev Neurosci 4:551–562
14. Wysocki CJ, Preti G (2004) Facts, fallacies, fears, and frustrations with human pheromones. Anat Rec 281:1200–1210
15. Lledo PM, Gheusi G, Vincent JD (2005) Information processing in the mammalian olfactory system. Physiol Rev 85:281–317
16. Keverne EB (2004) Brain evolution, chemosensory processing, and behavior. Nutr Rev 62:S218–S223
17. Hildebrand JG, Shepherd GM (1997) Mechanisms of olfactory discrimination: converging evidence for common principles across phyla. Annu Rev Neurosci 20:595–631
18. Ache BW, Young JM (2005) Olfaction: diverse species, conserved principles. Neuron 48:417–430
19. Tegoni M, Pelosi P, Vincent F, Spinelli S, Campanacci V, Grolli S, Ramoni R, Cambillau C (2000) Mammalian odorant binding proteins. Biochim Biophys Acta 1482:229–240
20. Ronnett GV, Moon C (2002) G proteins and olfactory signal transduction. Annu Rev Physiol 64:189–222
21. Buck LB (2004) Olfactory receptors and odor coding in mammals. Nutr Rev 62:S184–S188
22. Johnson BA, Woo CC, Leon M (1998) Spatial coding of odorant features in the glomerular layer of the rat olfactory bulb. J Comp Neurol 393:457–471
23. Gilad Y, Wiebe V, Przeworski M, Lancet D, Pääbo S (2004) Loss of olfactory receptor genes coincides with the acquisition of full trichromatic vision in primates. PLoS Biol 2:120–125
24. Shepherd GM (2004) The human sense of smell: are we better than we think? PLoS Biol 2:572–575
25. Malnic B, Hirono J, Sato T, Buck LB (1999) Combinatorial receptor codes for odors. Cell 96:713–723
26. Rolls ET (2001) The rules of formation of the olfactory representations found in the orbitofrontal cortex olfactory areas in primates. Chem Senses 26:595–604
27. Bensafi M, Rouby C, Farget V, Bertrand B, Vigouroux M, Holley A (2003) Perceptual, affective, and cognitive judgments of odors: pleasantness and handedness effects. Brain Cogn 51:270–275
28. Scott K (2005) Taste recognition: food for thought. Neuron 48:455–464

29. Breslin PA, Huang L (2006) Human taste: peripheral anatomy, taste transduction, and coding. Adv Otorhinolaryngol 63:152–190
30. Rolls ET (2004) Convergence of sensory systems in the orbitofrontal cortex in primates and brain design for emotion. Anat Rec 281:1211–1224
31. Cytowic RE (2002) Synesthesia: a union of the senses. MIT, Cambridge
32. Lledo P-M, Grubb M, Alonso M (2006) Adult neurogenesis and functional plasticity in neuronal circuits. Nat Neurosci Rev 7:179–193

Olfactometer

Definition
A device for delivering odorant stimuli with controlled odorant concentrations and durations.

►Brain States and Olfaction

Olfactory Acuity

►Olfactory Perception

Olfactory Adaptation

Definition
The decrease over time in the neural response to a continuous odorant presentation is known as olfactory adaptation.

►Glomerular Map
►Odorant

Olfactory Amygdala

Definition
Group of nuclei of the amygdaloid complex that receives olfactory information directly from the main olfactory bulbs or indirectly from other amygdaloid nuclei.

►Evolution of the Amygdala: Tetrapods
►Olfactory Bulb

Olfactory Aura

►Olfactory Hallucinations

Olfactory Awareness

►Olfactory Perception

Olfactory Binding Proteins

►Odorant-Binding Proteins

Olfactory Bulb

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Synonyms
Main olfactory bulb, as opposed to “accessory olfactory bulb”

Definition
The olfactory bulb is the first relay station in the olfactory pathway, situated at the rostral end of the brain. It receives sensory input from olfactory receptor neurons located in the nasal cavity and sends output fibers to a group of hemispheric regions collectively termed the olfactory cortex.

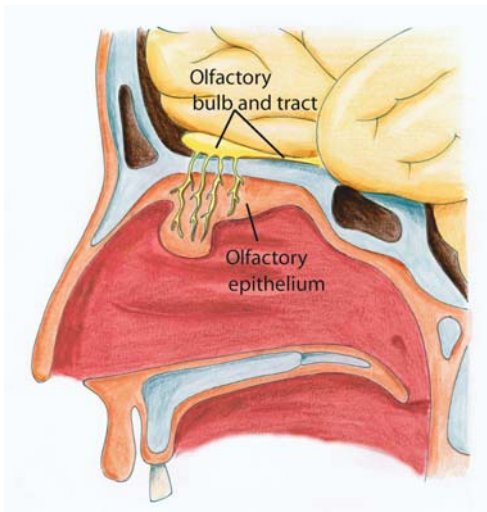
Characteristics

The olfactory bulbs develop from the ventral surface of the cerebral hemispheres and in the large majority of vertebrates they represent the most rostral extension of the neural axis. In apes and humans, however, the olfactory bulbs lie on the ventral surface of the frontal lobes, just above the nasal cavities, from which they are separated by the cribriform plate of the ethmoid bone (Fig. 1).

The unmyelinated axons of the olfactory nerve pass through this bone and reach the olfactory bulb, where they terminate in spheroidal regions of neuropil called glomeruli. Head trauma can lesion the olfactory nerve fascicles as they traverse the cribriform plate, resulting in anosmia. The olfactory tract leaves the posterior pole of the olfactory bulb. It contains the output projections of the bulb as well as afferent fibers originating from a variety of brain regions.

In most vertebrate species, the olfactory bulb is organized according to the same basic plan and, as in other cortical regions, it shows a laminated structure, consisting of seven concentric layers (Fig. 2).

The principal (output) neurons of the bulb are the mitral and tufted cells (M/T cells), which can be divided into multiple subtypes based on position, dendritic morphology and axonal projection patterns. Mitral and tufted cells receive excitatory sensory inputs in the glomerular layer and send their axons to different regions of the olfactory cortex. Apart from this straight-through pathway, there are other neurons that act locally and make predominantly inhibitory connections with the principal cells. Synaptic inhibition plays a crucial role in the processing of olfactory information before it is transmitted to the olfactory cortex (see below).



Olfactory Bulb. Figure 1 The olfactory bulb is a small ovoid structure that lies on the cribriform plate of the ethmoid bone. It receives input from olfactory sensory neurons located in the nasal cavity and projects to the olfactory cortex through the olfactory tract. (Courtesy of Dr. Alessandro Ciccarelli.)

It should be noted that neuronal excitation in the olfactory bulb is mediated primarily by glutamate, whereas GABA is the principal inhibitory neurotransmitter. In addition, the olfactory bulb is rich in several other neuroactive substances, which likely exert a neuromodulatory function.

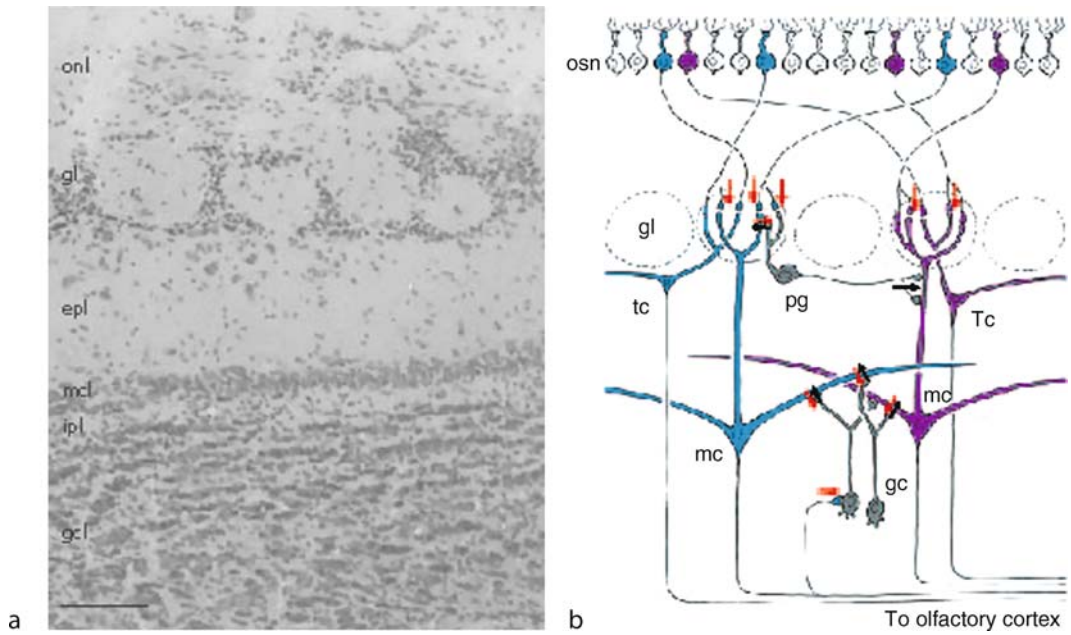
The circuit organization of the olfactory bulb can be conveniently separated into two distinct levels [2]. Sensory inputs from the ▶olfactory sensory neurons are first processed within the glomeruli, where they are subject to amplification and attenuation. The second level of processing involves reciprocal interactions between the principal neurons and local interneurons, which provide GABAergic inhibition through dendro-dendritic synapses.

Input Processing

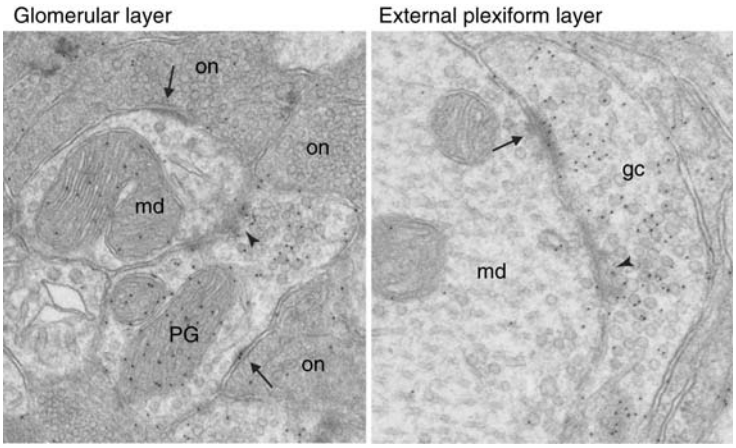
Within the glomeruli, sensory axons make excitatory synaptic connections with the apical dendrites of the output neurons and a heterogeneous class of intrinsic neurons called periglomerular cells (▶periglomerular cell in olfactory bulb) (PG) (Fig. 3).

In addition, PG cells are interconnected with M/T cells through dendro-dendritic synapses. Several types of dendro-dendritic synapses have been described, including excitatory synapses from M/T cells to PG cells, inhibitory synapses from PG cells to M/T cells, and synapses between distinct subtypes of PG cells. While there is no evidence for dendro-axonic synapses onto olfactory nerve axons, it has been shown that GABA and dopamine inhibit glutamate release from these axons by activating presynaptic receptors ($GABA_B$ receptors and dopamine D_2 receptors, respectively). It is likely that the paucity of glial barriers within the glomerular neuropil facilitates the diffusion of neurotransmitter and the occurrence of nonsynaptic interactions. The current model suggests that intraglomerular microcircuits contribute to regulate transmission from the olfactory nerve to M/T cells and thus serve as a gain control mechanism of incoming sensory signals.

A remarkable specificity exists in the projection pattern of olfactory receptor neurons to the glomeruli. First, each glomerulus is the site in which thousands of sensory axons converge on the dendrites of just ~20–50 relay neurons. A notable feature is that the axon of each sensory neuron terminates in only one glomerulus and, similarly, the apical dendrite of each principal neuron (mitral or tufted cell) arborizes into a single glomerulus. Second, all of the olfactory axons terminating in a glomerulus express the same odorant receptors (out of a repertoire of ~1,000 genes in rodents). Third, olfactory sensory neurons expressing a specific type of odorant receptor usually innervate two distinct glomeruli, which



Olfactory Bulb. Figure 2 (a) Coronal section of the rat olfactory bulb illustrating the laminar organization. The most superficial layer is the olfactory nerve layer (onl), which contains the axons of olfactory sensory neurons. Deep to the granule cells is a periventricular or subependymal layer (not visible in this micrograph), which contains migrating neuroblasts. gl: glomerular layer; epl: external plexiform layer; mcl: mitral cell layer; ipl: internal plexiform layer; gcl: granule cell layer. Scale bar: 100 μm. (b) Circuit diagram summarizing the basic synaptic organization of the olfactory bulb. Two glomerular units are shown, each receiving input from olfactory sensory neurons (osn) expressing a given type of odorant receptor and connecting to a subset of mitral cells (mc) and tufted cells (tc). Periglomerular cells (pg) and granule cells (gc) mediate feedback and lateral inhibition of principal neurons through axo-dendritic and dendro-dendritic synapses. *Red arrows* indicate excitatory synapses, and *black arrows* indicate inhibitory synapses. (Adapted from [1]; courtesy of Dr. Alessandro Ciccarelli.)



Olfactory Bulb. Figure 3 Synaptic connections of the olfactory bulb as shown by electron microscopy after postembedding immunogold labeling with an antiserum against GABA (courtesy of Dr. Patrizia Panzanelli). Gold particles of 10 nm identify GABA-immunopositive structures. In the glomerular layer, olfactory nerve axons (on) make asymmetrical synapses (*arrows*) with two dendritic profiles. One dendrite is GABA-positive and therefore belongs to a periglomerular cell (pg). The other dendrite (md) likely belongs to a mitral/tufted cell. Note that the pg dendrite also makes a dendro-dendritic synapse (*arrowhead*) with the md profile. External plexiform layer. A reciprocal dendro-dendritic synapse between a mitral cell dendrite (md) and a granule cell spine (gc) is shown. Note that the granule cell spine is GABA-positive. The mitral-to-granule synapse (*arrow*) is asymmetrical, whereas the granule-to-mitral synapse (*arrowhead*) is symmetrical.

are bilaterally symmetrical and similarly located in the olfactory bulbs of different animals [3]. Therefore, a glomerulus can be defined as a convergence center for inputs originating from a given type of odorant receptor. This specificity implies that glomeruli represent basic functional units, analogous to cortical columns, and that different odors are represented by different patterns of spatial activity in such glomerular units [1] (see glomerular map).

Inhibitory Control of Mitral/Tufted Cells

The second level of information processing in the olfactory bulb is based on reciprocal synapses between the principal neurons and the granule cells (Fig. 3). Granule cells are axonless neurons, whose cell bodies give rise to an apical dendrite that extends radially in the external plexiform layer [4]. The dendrites of granule cells are characterized by the presence of large spines (also called gemmules), that establish reciprocal synapses with the dendrites of M/T cells [5]. In these reciprocal connections, both sides of the synapse are dendrites capable of releasing neurotransmitter. The dendrites of M/T cells release glutamate and excite the spines of granule cells, which in turn release the inhibitory neurotransmitter GABA back onto the principal neurons (Fig. 2). As a result, activated M/T cells can inhibit themselves (feedback inhibition), as well as their neighbors (lateral inhibition).

There is compelling evidence that lateral inhibition is crucial in refining olfactory information, as it enhances the contrast between the activity of M/T cells connected to different glomerular units, and thus sharpens the tuning specificity of the output neurons to different odor molecules [1]. In other words, activation of M/T cells associated with one glomerulus results in inhibition of other glomerular units through the reciprocal dendrodendritic interactions. Therefore, the lateral inhibition mediated by granule cells enhances the contrast between strongly activated and faintly activated glomerular units and increases the specificity of individual M/T cells to odor molecules. Given that the basal dendrites of mitral cells have a projection field with a radius of about 1 mm, they potentially can influence the activity of glomerular units over long distances. This is consistent with experimental evidence that odor maps are widely distributed in the glomerular layer [6].

Lateral inhibition is also important for synchronizing the output responses of M/T cells connected to functionally related glomeruli. It has been known for a long time that stimulation with odor molecules elicits γ-frequency (30–80 Hz) oscillations of local field potentials, reflecting synchronized spike discharges of the principal neurons. This synchronization likely serves as a mechanism for temporal summation of signals from different glomerular units, and may play an important role in odor discrimination [7]. Of particular interest is the possibility that plastic changes in the strength of dendro-dendritic synapses may represent one mechanism underlying olfactory learning.

Other Neuronal Populations

In addition to PG cells and granule cells, there is a relatively small population of short-axon cells, which are distributed in the glomerular and granule cell layers. Recent studies suggest that interglomerular interactions mediated by short-axon cells represent a mechanism by which activated glomeruli can influence the activity of other glomerular units and contribute to enhance the spatial responses to odors [8]. In addition, one type of short-axon cell located in the granule cell layer provides GABAergic inhibition onto granule cells and therefore can control the strength of feedback and lateral inhibition onto the principal neurons [9].

Centrifugal Afferents

The olfactory bulb receives a prominent innervation by centrifugal fibers from a variety of sites in the brain. The best characterized are cholinergic fibers arising from the basal forebrain and noradrenergic and serotoninergic fibers arising, respectively, from the *locus coeruleus* and the mesencephalic raphe nucleus. These centrifugal afferents mediate a considerable degree of control over olfactory processing, which seems to be important for adapting olfactory function to different behavioral states. Of particular interest is the action of noradrenaline, which suppresses granule cell inhibition of M/T cells. Noradrenergic modulation of dendro-dendritic inhibition has been involved in some forms of olfactory learning.

Parallel Processing of Olfactory Stimuli

As in other sensory systems, the olfactory bulb contains several parallel pathways for processing olfactory information. An obvious case is the accessory olfactory bulb, a structure present in most terrestrial vertebrates that receives sensory inputs from the vomeronasal organ. Within the main olfactory bulb, there is evidence for specialized glomerular units that process certain types of olfactory stimuli. For instance, the so called "modified glomerular complex" has been implicated in suckling behavior in neonatal animals. Mitral and tufted cells also appear give rise to parallel output pathways from the olfactory bulb. These neurons interact with different subpopulations of granule cells and project their axons to different cortical regions [10]. However, our understanding of how mitral and tufted cells process distinct aspects of olfactory information is still preliminary.

Plasticity

The olfactory bulb is one of the few brain regions in which neurogenesis in maintained throughout life.

Bulbar interneurons are continuously replaced from a population of stem cells located in the subventricular zone of the lateral ventricle. Neuroblasts generated in this area migrate along the rostral migratory stream to the olfactory bulb, where they complete their differentiation into GABAergic neurons. Similarly, olfactory sensory neurons undergo continuous turnover during adult life. Remarkably, these neurons can reestablish functional synaptic connections with their target cells in the olfactory bulb. This degree of plasticity is unmatched in the brain and makes the olfactory bulb a unique model for studying the mechanisms of neural development and cell replacement.

References

1. Mori K, Nagao H, Yoshihara Y (1999) The olfactory bulb: coding and processing of odor molecule information. Science 286:711–715
2. Shepherd GM (2004) Olfactory bulb. In: Shepherd GM (ed) The synaptic organization of the brain, 5th edn. Oxford University Press, New York, pp 165–216
3. Vassar R, Chao SK, Sitcheran R, Nuñez JM, Vosshall LB, Axel R (1994) Topographic organization of sensory projections to the olfactory bulb. Cell 79:981–991
4. Shepherd GM, Chen WR, Willhite D, Migliore M, Greer CA (2007) The olfactory granule cell: from classical enigma to central role in olfactory processing. Brain Res Rev 55:373–382
5. Price JL, Powell TPS (1970) The synaptology of the granule cells of the olfactory bulb. J Cell Sci 7:125–155
6. Leon M, Johnson BA (2003) Olfactory coding in the mammalian olfactory bulb. Brain Res Rev 42:23–32
7. Laurent G (2002) Olfactory network dynamics and the coding of multidimensional signals. Nat Rev Neurosci 3:884–895
8. Aungst JL, Heyward PM, Puche AC, Karnup SV, Hayar A, Szabo G, Shipley MT (2003) Center-surround inhibition among olfactory glomeruli. Nature 426:623–629
9. Pressler R, Strowbridge B (2006) Blanes cells mediate persistent feedforward inhibition onto granule cells in the olfactory bulb. Neuron 49:889–904
10. Zou Z, Horowitz LF, Montmayeur JP, Snapper S, Buck LB (2001) Genetic tracing reveals a stereotyped sensory map in the olfactory cortex. Nature 414:173–179

Olfactory Bulb Glomerulus

Definition

An olfactory glomerulus is a compartmentalized mass of neuropil in the glomerular layer of the olfactory bulb that contains synapses between olfactory sensory neuron axon terminals and dendrites of both projection neurons (mitral and tufted cell apical dendrites) and local periglomerular cell inhibitory interneurons. Glomeruli also contain numerous dendrodendritic synapses between mitral or tufted cells and both periglomerular and so-called short-axon cells. A typical rodent olfactory glomerulus receives convergent projections only from sensory neurons expressing the same odorant receptor gene. At the neuronal circuit level, an individual glomerulus in the olfactory bulb may function as a molecular-feature detecting unit.

►Flavor
►Glomerular Map
►Olfactory Bulb
►Olfactory Bulb Mitral Cells
►Olfactory Sensory Neuron
►Periglomerular Cells in Olfactory Bulb

Olfactory Bulb Granule Cells

Definition

These are a large population of small GABAergic interneurons in the vertebrate olfactory bulb that do not receive sensory input directly. They form dendrodendritic reciprocal synapses with mitral cell lateral dendrites and also receive axodendritic synapses from mitral cell axon collaterals and centrifugal fibers. Most of their inputs are glutamatergic, but they also receive GABAergic inputs. Most olfactory bulb centrifugal inputs target the granule cells.

►Olfactory Bulb
►Olfactory Bulb Mitral Cells

Olfactory Bulb Mitral Cells

Definition

Glutamatergic projection neurons lying in the mitral cell layer of the olfactory bulb. They receive direct input from olfactory sensory neuron terminals in olfactory bulb glomeruli, and project directly to olfactory cortex. They also have multiple, complex interactions with olfactory bulb interneurons, both periglomerular cells and granule cells, through conventional and dendrodendritic synapses.

►Olfactory Bulb
►Olfactory Cortex
►Olfactory Sensory Neuron

Olfactory Code

►Odor Coding

Olfactory Coding

►Odor Coding

Olfactory Cortex

Gilles Sicard
Centre Européen des Sciences du Goût, Dijon, France

Synonyms

Downstream neural structure of the olfactory bulb

Definition

Referring to multiple structures receiving olfactory information and presenting the classical cyto-architecture of nervous cortex, "olfactory cortices" is a more correct definition of the topic of this article.

Stock of knowledge. Details of the ►primary cortical projections of the olfactory system indicate the diversity of the structures that are directly connected to the olfactory bulb neurons (Fig. 1).

Characteristics

The graph is soon a divergence from the canonical hierarchical organization of a sensory pathway. The bulbar output is conveyed by the lateral olfactory tract. On the functional point of view, we do assume that a topographical representation of the olfactory stimulus based on the chemical features takes place in the glomerular layer of the olfactory bulb.

From the receptor level, the primary ►olfactory cortex is reached through two synapses only. The receptor neurons are connected to mitral and tufted cells in the olfactory bulb. These relay neurons feed the pyramidal cells of the cortex, a three-layered paleocortex. The primary olfactory projections are annexed to the ►limbic system, an associative area. This system plays a role in social and emotional processing and supports some of the mechanisms of the memory.

Two neurons, two synapses: It is noticeable that this short pathway bypasses the thalamus before displaying cortical representations of the stimulus. This peculiar arrangement differing from those observed in other sensorial modalities can be explain by the fact that olfactory modality got ahead the emergence of the thalamic structures in the phylogenesis. On a functional point of view, this also means that probably in the olfactory system the processes fulfilled by the thalamus are implemented in other structure(s), and logically, in the downstream structures (thus the olfactory bulb) and/or the structures described the present chapter. It looks likely as both olfactory bulb and olfactory cortices receive modulating influences from diverse centers, including for instance the arousal or the satiety control systems.

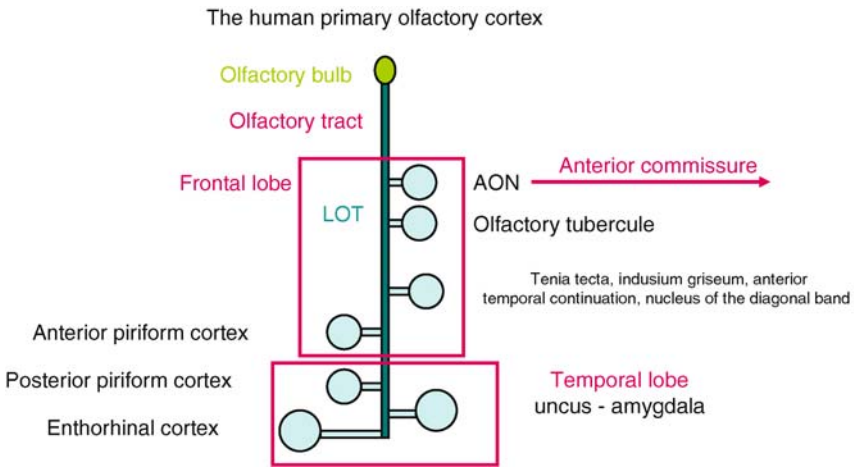
Focusing on the functional properties of the olfactory cortices, they are considered both as the targets of relay neurons from the olfactory bulb and as the origin of neurons contacting neocortical associative territories such as the orbito-frontal cortex, the neocortical temporal cortex … and even parts of the thalamus!

The ►primary olfactory cortex includes contiguous or dispersed structures in the medial aspect of the temporal lobe of the brain which homologous equivalents are not easy to identify among different species. In order to describe the functions of the olfactory cortex, we get information from different animal models, rat, mouse, rabbit or frog, including man. In the view of this complexity, the terminology itself can be misleading: For instance the anterior olfactory nucleus which is funded by the fibers of the lateral olfactory tract, is a true cortex, characterized by the presence of pyramidal neurons. For those reasons, we have limited the description to the main structures: the anterior olfactory nucleus, the piriform cortex, the olfactory part of the amygdala and the entorhinal cortex. A ►secondary olfactory cortical area taking information from ►primary olfactory cortices, the orbito-frontal cortex will be also envisaged in the article.

With the olfactory cortex processing, important integrations of the olfactory signal follows the first sharpening of the information captured from the chemical environment by the receptor organ. If in the olfactory bulb the chemical nature of the stimulus is decomposed (de-constructed representation of odorants), in the olfactory cortex several tasks of reconstruction (re-constructed representation) take place, add memorized information and finally these levels of processing tend to confer a "meaning" to the actual olfactory message.

Primary Cortical Projections

Anterior olfactory nucleus. Natural odorants are mixtures of chemicals. To imagine the integrative processes of the neurons, one can test how the neurons are responding to chemical mixtures and to their isolated components. While bulbar neurons show a



Olfactory Cortex. Figure 1 The human primary olfactory cortex: The hierarchical representation of the olfactory pathway describes a multi-unit network: The olfactory tract is constituted of the mitral and tufted-neuron axons, the relay neurons directly connected to the receptor neurons from the olfactory receptor organ in the olfactory bulb. By this pathway a number of cortical structures receive direct sensory inputs. They are distributed in different parts – frontal temporal – of the cerebral cortex. These primary cortical elements are largely interconnected and receive modulations from different higher centers (arousal, satiety…). The first part, anterior olfactory nucleus and piriform cortex are concerned by sharpening of the sensory message. The other units are involved in control of emotional responses, behavioral responses to odorant stimulations and in olfactory learning.

sparse responsiveness they show high selectivity and they often respond to only one of the components in a mixture. In the anterior olfactory nucleus, the majority of neurons can respond to mixture of dissimilar chemicals and to their isolated components. In addition, the responses to the mixture exceed the simple sum of the responses to each of its components [1]. These properties point out a first kind of integrative process that the neuronal populations of ►primary cortical olfactory level are able to realize: This is a simple sharpening of the sensory input message.

Piriform cortex. Extensively connected with higher-order cortical areas, the piriform cortex received also direct afferences from the olfactory bulb. The receptor fields of its neurons have been characterized by neuronal tracing, giving a spatial idea of the coding of the odorant stimuli [2] while electrophysiological recording of the neuronal responses to odorants gave a functional view [3]. As a ►primary cortex, it could take part to the extraction of specific features from the olfactory message, thus used the combinatorial analytic representation of the sensory signal provided by the olfactory bulb. At this level, some neurons require particular combinations of chemicals to respond, thus suggest a combination of signals from distinct samples of bulbar neurons [4]: The cortex plays a role in discrimination of odorant signals. Nevertheless, at this early level, some modulations of the neuronal responses in behaving rats by non olfactory information (reward, expectation) were found, adding associative functions to its competences. In that sense, this "►primary" cortex differs from primary cortices (►primary, secondary cortices) of the other sensorial modalities, which are rather dedicated to sharpen the input message. The olfactory piriform cortex must be regarded as a piece of olfactory learning and memory [5] It is of great importance to note that the receptive fields of the neurons in this cortex change with the experience: This property is indicative of upper-stream associative areas in the other sensorial modalities.

According to neuronal tracing, the partial overlapping of the projections from different receptor channels in the piriform cortex suggests that the cortex is able to merge different elements of the peripheral signal. In the anterior olfactory nucleus or in anterior piriform cortex, the selectivity of neurons to diverse chemical or perceptual categories appears to be broader than that of the bulbar relay neurons. This is true assuming that, due to the functional convergence of receptor neurons on bulbar glomeruli, the output neurons, mitral and tufted cells, have relatively narrow ►selectivity profiles. (We must notice some discrepancy about the chemical selectivity of the bulbar neurons reported in different studies). Nevertheless, the complex selectivity profiles of the cortical output neurons means that these neurons integrate several odorant features.

Odorant quality coding in the olfactory piriform cortex. Tracing the projections area of the output bulbar neurons, it is possible to discriminate an anterior part and an posterior part of the piriform cortex [2]. This is confirmed by functional observations of the spatial organization of the responses to hedonic contrasted chemical stimuli in human [6]. While the

anterior part seems to encode the chemical features, the posterior part could discriminate stimuli along a qualitative dimension, i.e. their odor. Following the partial functional convergence shown by the bulbo-cortical relationships, the anterior piriform Cortex could reconstruct the complex environmental stimuli that have been decomposed by the topographic arrangements of the bulbar projections of the hundreds of specific olfactory receptors. The mechanisms or the rules of this reconstruction are not known. In this debate, the representation suggested by the topographical combinatorial theory plays a central role. However, one must notice that several studies on electrophysiological reports confirms that the selectivity of the bulbar neurons is scarce, but indicate that these neurons convey activations elicited by very different chemical structures [3,4]. The integration of this information on the discrimination processing by the cortical neuronal population must be further examined.

Contributions of olfactory cortices to behavioral controls. Several other olfactory cortices, recruiting even a larger amount of influences, are also directly connected to the olfactory bulb.

The amygdala is in fact a series of nucleus, receiving inputs from multiple ascending sensory pathways, including olfactory, gustatory, visual, auditory and visceral information, more or less directly from the sensory organ, thus after more or less stages of treatment. Here again the afferent olfactory pathway is the shortest. Extending influences on the hypothalamus, the medulla or the spinal chord, the amygdala is implicated in the modulation of the visceral functions in relation with emotional status. By its connections with the nearest olfactory structures in the rostral temporal lobe, it modulates their activity according to the mood or the emotional life of the animal.

Different implications of the olfactory amygdala on animal behavior have been investigated. In fact the different cortical olfactory structures, including amygdala, entorhinal cortex, perirhinal cortex are interconnected: Consequently, the exerted controls supported by olfactory cues are the effects of a network of specialized structures.

Fear olfactory conditioning or olfactory conditioned food or beverage aversion are examples that can give an idea of the functions of these networks.

Differential implication of theses area has been shown in their contribution to olfactory and contextual fear conditioning. The amygdala participates in the acquisition and the expression of fear conditioned to both an olfactory conditioned stimulus and to the training context. The perirhinal cortex participates to olfactory, but not contextual, fear conditioning. In addition, the perirhinal cortex seems to play a prominent role in recognition of the conditioned stimuli [7].

Another behavioral register is intensively explore: the ►odor conditioned aversion. Several parts of the primary olfactory cortex are implicated in its mechanisms. For instance, the effects of lesions of the entorhinal cortex are coherent with a role of this cortex in conditioned odor-aversion learning. A subdivision of this cortex as indicated by the heterogeneity of its connections is confirmed by functional arguments. The lateral part only is involved in the control of the olfactory memory trace during the conditioned olfactory aversion process. In addition the data are consistent with the idea that the lateral part represent the input of the structure while the medial part represent the output to hippocampus [8]. Here again, an olfactory cortex network is implicated. Interestingly, it has been shown that electrophysiological stimulations of the lateral entorhinal cortex is able to inhibit the olfactory input from the amygdala.

Integration. The primary olfactory cortex is of course inserted in a larger cerebral network and is a target for numerous modulating impacts. For instance, in the rat, 800 neurons from the anterior hypothalamus are secreting the peptide ►GnRH. Influence of these neurons on primary cortical structures of the olfactory system: Some neurons of the anterior olfactory nucleus, anterior and posterior piriform cortex, anterior cortical amygdaloidal nucleus and the lateral entorhinal cortex as it is shown by anterograde barley lectin labeling receive projection of the hypothalamic GnRH neurons [9]. This particular pathway illustrates one of the nervous supports of the integration of the olfactory sensitivity in the physiology and behavior. Odors signals or pheromones could have effects on the neuroendocrine status but in return, mediated by cerebral feed-back loops under the influence of sexual or reproductive hormones, other parts of the brain could modulate the olfactory abilities.

Secondary Cortical Areas

Axons of neurons from the primary cortical areas reached a number of others brain structures. Focusing on the olfactory sense, the orbito-frontal cortex and temporo-lateral neocortical structures are the most extensively studied. At this level, it is a neocortex that receives and processes the olfactory information.

As a main property, the *olfactory orbito-frontal cortex* receives afferent axons from several other sensorial sources. Among the other important influences, the cortex receives information from the gustatory pathway and had been explored as a centre related to feeding behavior and food choice. As seen using brain imagery, the orbito-frontal cortex is consistently activated by olfactory stimuli [10] and is sensitive to context. These are functional characteristics of a secondary cortex (primary, secondary cortices). Moreover, in this cortex, we find converging fibers from multiple sensory areas, i.e. the primary somatosensory cortex, the primary taste cortex (frontal operculum), the inferior temporal visual cortex, the striatum, the amygdala and the olfactory piriform

cortex. Additional fibers from ►hunger neurons confer to this area a central role in the food-related evaluation of odor and taste. Some neurons of this cortex are responsive to odor and taste for instance. Some of them decrease their response to food eaten to satiety.

This last remark illustrates an important view of the sensory physiology: The multimodality appears as an ultimate refinement of the environment representation. In the orbito-frontal cortex, representations of taste and other mouth feels, smell sight are converging. This is why the representation of food stimuli, and finally appetite, are modulated by sensory-specific controls, involving olfactory cues.

References

1. Lei H, Mooney R, Katz LC (2006) Synaptic integration of olfactory information in mouse anterior olfactory nucleus. J Neurosci 26:12023–12032
2. Zou Z, Li F, Buck LB (2005) Odor maps in the olfactory cortex. Proc Natl Acad Sci 102:7724–7729
3. Davidson IG, Katz LC (2007) Sparse and selective odor coding by mitral/tufted neurons in the main olfactory bulb. J Neurosci 27:2091–2101
4. Zou Z, Buck LB (2006) Combinatorial effects of odorant mixes in olfactory cortex. Science 331:1477–1481
5. Ross RS, Eichenbaum H (2006) Dynamics of hippocampal and cortical activation during consolidation of a nonspatial memory. J Neurosci 26:4852–4859
6. Gotfried JA, Winston JS, Dolan RJ (2006) Dissociable codes of odor quality and odorant structure in human piriform cortex. Neuron 49:467–479
7. Otto T, Cousens G, Herzog C (2000) Behavioral and neuropsychological foundations of olfactory fear conditioning. Behav Brain Res 110:119–128
8. Ferry B, Ferreira G, Traissard N, Majchzak M (2006) Selective involvement of the lateral entorhinal cortex in the control of the olfactory memory trace during conditioned odor aversion in the rat. Behav Neurosci 120:1180–1186
9. Boehm U, Zou Z, Buck LB (2005) Feedback loops link odor and pheromone signaling with reproduction. Cell 123:683–695
10. Zatorre RJ, Jones-Gotman M, Evans AC, Meyer E (1992) Functional localization and lateralization of human olfactory cortex. Nature 360:339–340

Olfactory Cortex – Piriform Cortex

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Synonyms

Piriform cortex; Pyriform cortex; Prepyriform cortex

Definition

At a very general level the term "olfactory cortex" can be used for all those areas in the rostro-ventral portion of the forebrain which receive direct projections from the olfactory bulb. These areas are: the anterior olfactory nucleus (also called anterior olfactory cortex), the olfactory tubercle, the ►piriform cortex, the entorhinal cortex, the insular cortex and the amygdala [1]. More specifically, however, the term has been – and will be, in the context of this entry – used in reference to the piriform cortex, by far the largest cortical area primarily involved in perception and learning of olfactory stimuli.

Characteristics

Introduction

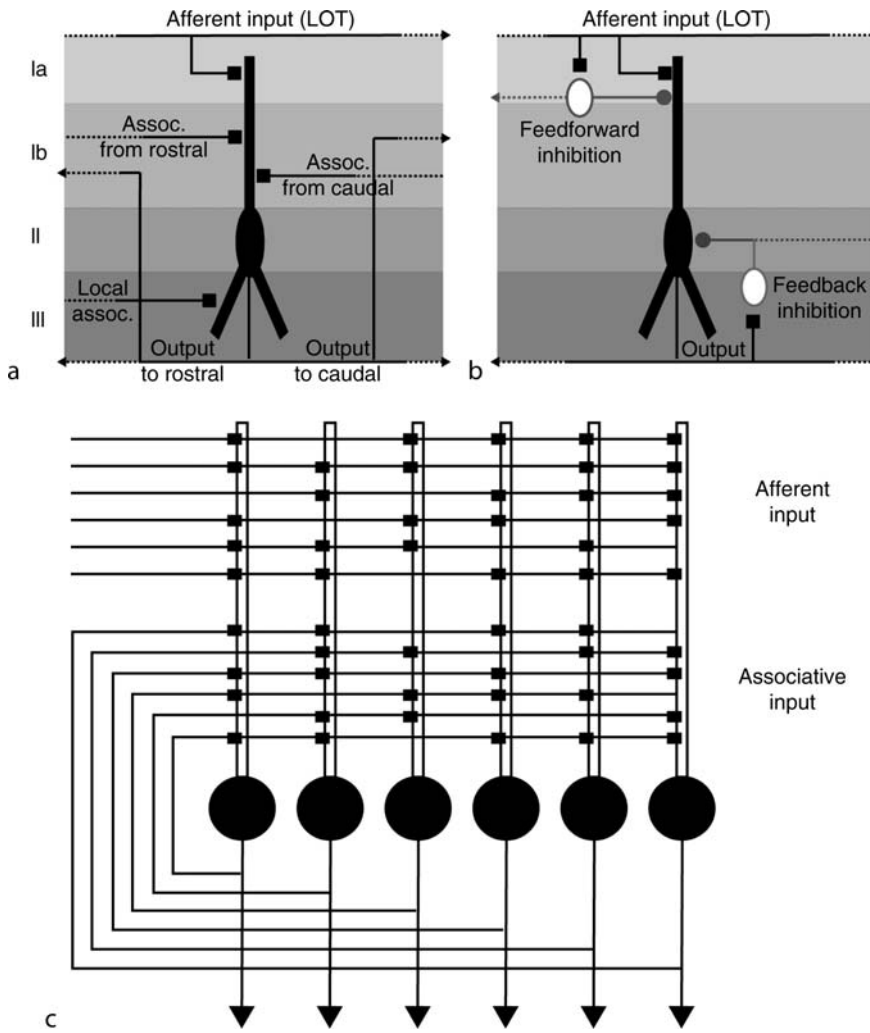
The piriform cortex, also referred to as paleocortex for its old phylogeny, has an evolutionarily well-conserved cellular and synaptic organization [2]. Differently from the neocortex, which appeared more recently in evolution and has a complex multilayered architecture [3], the olfactory cortex is organized in a simpler and experimentally more tractable three layered architecture. Despite this different organization, however, the olfactory cortex and neocortical sensory areas share many functional properties [4]. The study of the olfactory cortex offers, therefore, the unique opportunity to understand how general properties of cortical organization and functioning can be produced by simpler and phylogenetically older structures. As such, a deep understanding of the olfactory cortex will not only help us in the study of olfaction, but also likely advance our knowledge of the general functional organization of the cerebral cortex [4].

Cytoarchitecture

The olfactory cortex is vertically organized into three layers, each characterized by a different composition of cell types and axonal fibers which spread horizontally [1]. Layer I, the most superficial, is a low cell-density layer composed, in its most superficial part (Ia), by afferent sensory fibers horizontally organized and coming from the olfactory bulb through the lateral olfactory tract (LOT), and in its deeper portion (Ib) by cortico-cortical (associative) horizontal axons coming from other parts of the olfactory cortex and other olfactory areas. Afferent and associative fibers contact the apical dendrites of excitatory neurons located in layer II and III and dendrites of inhibitory interneurons. The next layer, layer II, is composed by densely packed somata of excitatory (pyramidal and semilunar) and inhibitory (stellate and bipolar) cells. Finally, layer III shows a gradual decline in cell density with increasing distance from layer II, and contains somata and dendrites of deep pyramidal neurons, multipolar interneurons, basal dendrites of layer II pyramidal cells and cortico-cortical associative fibers.

As in the case of neorcortex, the circuit of the olfactory cortex is organized around principal excitatory neurons. The different subtypes of excitatory neurons, which are characterized by distinct functional properties, are all embedded in the same, apparently stereotyped, circuit (Fig. 1a) [1]: pyramidal and semilunar neurons receive feed-forward excitatory input from mitral cells in the olfactory bulb and recurrent associative excitatory inputs from other principal neurons within the olfactory cortex, in turn, they send their outputs within the olfactory cortex itself and to other cortical areas (entorhinal and perirhinal cortices, hippocampus, amygdala and orbitorfrontal cortex among them [1]).

Principal neurons are also embedded into two inhibitory circuits (Fig. 1b) [1]: one of which is based on a feedforward input from inhibitory cells in layer I directly activated by afferents from the bulb, the second is a feedback inhibitory loop carried by inhibitory interneurons in layer Ib and III which are activated by associative recurrent fibers from pyramidal cells. Bipolar interneurons, which receive both afferent and associative inputs can take part to both circuits. This



Olfactory Cortex – Piriform Cortex. Figure 1 Architecture of the olfactory cortex and of an autoassociative network. (a) Excitatory inputs and outputs of a pyramidal neuron. All fibers are organized vertically and segregated in different layers. Afferent inputs come from the LOT, associative inputs can come from distant or be local. Black squares represent excitatory synaptic contacts, lines with arrows represent the outputs of the circuit or, in case of the LOT, the signal propagating caudally. (b) Simplified inhibitory circuit impinging on pyramidal neurons. White circles are feedforward and feedback inhibitory interneurons; grey circles represent inhibitory contacts. (c) Schematic of an autoassociative network: synaptic contacts from afferent and associative inputs are represented as black squares contacting the neural units. (a) and (b) modified from [1].

structure, which is the foundation of the olfactory cortex basic electrophysiological behavior, is however far from rigid and immutable. Previous patterns of activity, sensory experience, as well as neuromodulators play a major role in inducing synaptic plasticity at different sites, shaping this architecture and resulting in different functional configurations [5].

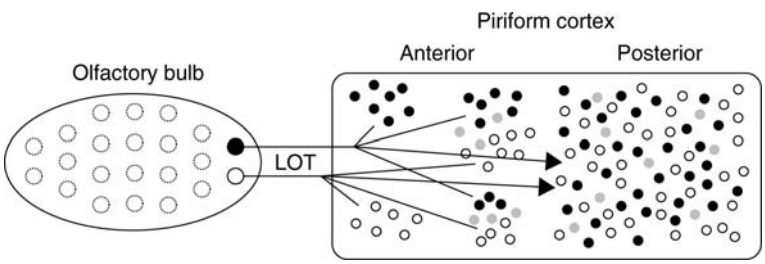
Functional Organization

The characteristic extension of the associative system, and the suggestion that afferent inputs might be diffuse and without major topographical organization lead to the formulation of the most influential functional view of the olfactory cortex to date [5,6]. According to this view, the olfactory cortex can be seen as a biological analogue of a typical autoassociative artificial neural network. These types of artificial neural networks, characterized by neural units (or nodes) receiving sparse external inputs and also recurrent autoassociative inputs coming from the nodes themselves (Fig. 1c), are ideally suited for performing tasks analogous to those thought to be performed by the olfactory cortex: they can detect and discriminate complex mixtures of odors, reconstruct known mixtures on the basis of some of its components and dynamically switch between processing, storing and recalling of inputs and memories. Learning and dynamics are ensured, in this artificial network as well as in the olfactory cortex, by plasticity and neuromodulation of afferent and associative synapses [5].

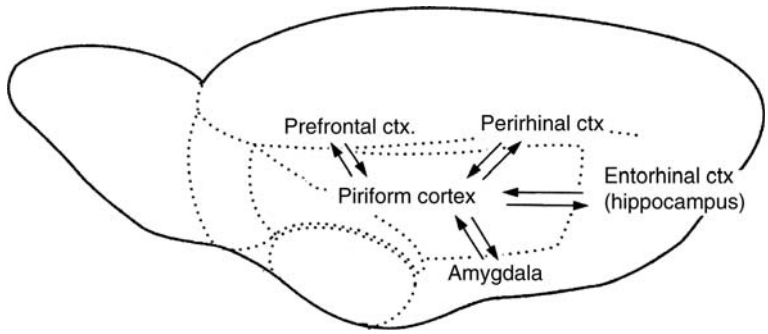
This functional view of the olfactory system has been recently challenged by new results coming from genetic tracing and showing that the organization of the cortex is not as homogeneous as previously believed, but rather individual odors are processed by spatially organized quasi-specific subsets of neurons (Fig. 2) [7].

These results have given strength to a different view of the cortex, according to which odors are represented by the feedforward activation of specific sets of partially overlapping neural populations (labeled lines) and that complex mixtures are coded – and learned – by patterns of coactivation of the subset of neurons receiving convergent inputs.

In reality these two views, the distributed/associative versus the labeled-line/feedforward, can be integrated in several ways. The olfactory cortex is divided into an anterior part and a posterior part [1]: the anterior olfactory cortex is principally driven by afferent bulbar inputs which are functionally organized into large (and to some degree also overlapping) patches; the posterior part, on the other hand, is less driven by afferent inputs and they are organized in a more distributed fashion. Taking this evidence into account it is possible to imagine that the organization of each of the two subdivisions could be biased toward one or the other coding scheme. Additionally, and more importantly, while genetic tracing shows that specific cells code for a specific odor, the degree of convergence seen in the cortex for inputs carrying information for different odors is remarkable and compatible with the model of an autoassociative network. Therefore some of the properties of the autoassociative framework, like the importance of associative fibers, the complex temporal evolution of processing due to cortico-cortical associative connections and the ability to dynamically switch between different network configurations, can be incorporated in the feedforward theory to add complexity, flexibility and ecological realism. Recent work employing simultaneous recordings from multiple neurons in the olfactory cortex has shown that odors activate spatially scattered populations of neurons, which are only partially non-overlapping, and that the patterns of activity become more complex and overlapping as the time course of the response evolves [8]. These results provide support to the fact that the simple labeled line feedforward processing scheme needs to be integrated into a more complex distributed coding paradigm.



Olfactory Cortex – Piriform Cortex. Figure 2 Topographical organization of bulbar inputs to the olfactory cortex. Outputs from different glomeruli project to partially overlapping but overall spatially distinct patches of neurons in the anterior olfactory cortex. Projections to the posterior cortex are more distributed. Black and white circles in the piriform cortex represent cells activated by distinct glomeruli, grey circles are cells receiving convergent inputs. Modified from [7].



Olfactory Cortex – Piriform Cortex. Figure 3 Bidirectional connections between the piriform cortex and other high order cortical areas. Modified from [1].

Macroscopic Dynamics

Regardless of the coding scheme, electrophysiological recordings from the olfactory cortex of animals engaged in purposeful behaviors have revealed an even more complex picture: odor processing is inherently dependent on the behavioral and environmental context. Pioneering work from Walter Freeman [see for a review 9], for instance, has shown that the olfactory cortex produces different patterns of activity depending on the physiological and cognitive state of the animal: odors presented to hungry or thirsty cats, for instance, produce oscillatory activity larger than the one evoked by the same stimuli presented to satiated animals. These and other more recent observations imply that olfactory coding mechanisms are constantly modulated by dynamic activity from other brain areas involved in different cognitive states [10]. The anatomy is consistent with this view, as the olfactory cortex receives direct or indirect inputs from high order brain areas, such as the hippocampus, entorhinal cortex, orbitofrontal cortex, amygdala and hypothalamus; additionally several brainstem neuromodulatory nuclei provide noradrendergic, cholinergic, serotoninergic and dopaminergic modulation [1]. These projections are the anatomical substrate through which emotional states (sustained by amygdala), memories (hippocampus), expectations (amygdala and orbitofrontal cortex), hunger and thirst (hypothalamus) and arousal levels (neuromodulatory nuclei) could influence patterns of spontaneous and odor-evoked olfactory cortex activity (Fig. 3).

Summary

The olfactory cortex is the largest area devoted to processing of olfactory information. It shares many functional properties with other sensory areas, but it has the advantage of a relatively simpler organization. The enhanced experimental and conceptual tractability deriving from this simpler organization has favored the use of the piriform cortex as a study model for complex issues such as sensory coding and behavioral modulation of sensory responses. Future studies of the olfactory cortex will therefore help us understand not only olfaction, but also fundamental functional properties of sensory systems in general.

References

1. Neville KR, Haberly LB (2004) Olfactory cortex, In: Shepherd GM (eds), The synaptic organization of the brain. Oxford University Press, New York, pp 415–454
2. Haberly LB (1990) Comparative aspects of olfactory cortex, In: Jones EG, Peters A (eds) Comparative structure and evolution of cerebral cortex. Cerebral cortex. Plenum, New York, pp 137–166
3. Aboitiz F, Morales D, Montiel J (2003) The evolutionary origin of the mammalian isocortex: towards an integrated developmental and functional approach. Behav Brain Sci 26:535–552; discussion 552–585
4. Fontanini A, Bower JM (2006) Slow-waves in the olfactory system: an olfactory perspective on cortical rhythms. Trends Neurosci 29:429–437
5. Linster C, Hasselmo ME (2001) Neuromodulation and the functional dynamics of piriform cortex. Chem Senses 26:585–594
6. Haberly LB, Bower JM (1989) Olfactory cortex: model circuit for study of associative memory? Trends Neurosci 12:258–264
7. Zou Z et al (2001) Genetic tracing reveals a stereotyped sensory map in the olfactory cortex. Nature 414:173–179
8. Rennaker RL et al (2007) Spatial and temporal distribution of odorant-evoked activity in the piriform cortex. J Neurosci 27:1534–1542
9. Freeman WJ (2001) Neurodynamics: an exploration in mesoscopic brain dynamics. Springer-Verlag, New York
10. Kay LM, Freeman WJ (1998) Bidirectional processing in the olfactory-limbic axis during olfactory behavior. Behav Neurosci 112:541–553

Olfactory Cue

►Odor

Olfactory Discernment

►Olfactory Perception

Olfactory Disorders

►Smell Disorders

Olfactory Ensheathing Cells

Definition

Glial cells unique to the olfactory system, which ensheath the axons of the olfactory receptor neurons, without providing full myelination. The primary olfactory system is an unusual tissue in that it can support neurogenesis throughout life. This unique regenerative property depends, in part, on the presence of olfactory ensheathing cells, and has recently been shown to have a remarkable ability to repair spinal cord injury.

►Myelin
►Regeneration

Olfactory Epithelium

Definition

The olfactory epithelium is a specialized chemosensory portion of the nasal epithelial tissue that contains the olfactory sensory neurons. In humans, it occupies an area of about 5 cm^2 covering the posterior part of the roof of each nasal cavity and the superior nasal concha. The olfactory epithelium is composed of three types of cells: the olfactory sensory neurons, which transduce odorants into electrical signals, the supporting, glia-like cells and the basal cells, which are stem cells capable of replacing the olfactory cell population. Because of this regenerative capacity, damage to the olfactory epithelium may results in only temporary anosmia.

►Anosmia
►Evolution of Olfactory and Vomeronasal Systems
►Odorant
►Olfactory Sensory Neuron

Olfactory Glomerular Module

Definition

Also known as a glomerular domain, an olfactory glomerular module is a spatial cluster of olfactory glomeruli responding to chemically similar odorant stimuli. Spatial clustering of glomeruli with similar response profiles into glomerular modules may facilitate the use of local center-surround lateral inhibitory networks to restrict the molecular receptive range of mitral cell projection neurons to a more narrow range of stimuli. Thus, odorants that stimulate strongly overlapping sets of receptors may be represented by a smaller set of mitral cells.

►Glomerular Map
►Odorant
►Olfactory Bulb Mitral Cell
►Olfactory Glomerulus

Olfactory Glomerulus

Definition

►Olfactory Bulb Glomerulus

Olfactory-guided Behavior Studies

►Behavioral Methods in Olfactory Research

Olfactory Hallucinations

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Synonyms

Olfactory aura; Phantosmia

Definition

An olfactory hallucination is a subjective experience of smell, which occurs in the absence of an appropriate stimulus.

Characteristics

Olfactory hallucinations (OHs) can occur in normal participants, as an unaccompanied primary symptom (phantosmia), and as a secondary symptom in a range of medical and psychiatric disorders [1]. Whilst the term simple or complex has been used to classify hallucinations in the auditory and visual domains (e.g., spots of light vs. an elephant) this distinction does not readily transfer to OHs. Most OHs appear to be complex, in that the person perceives a fully formed odor object (e.g., the smell of cooked chicken) rather than an unformed olfactory event. However, something akin to the simple versus complex distinction may be reflected in the integration of the OH with other concurrent events (real or hallucinated). For example, a Charles Bonnet syndrome patient reported hallucinating both a visual image of a girl *and* the smell of her perfume.

There are several other characteristic features of OHs. First, they show the same range of odor qualities (what it smells like) as real odors and they vary in intensity and hedonics, with most OHs reported as unpleasant. Second, when an OH is first experienced, they may be accompanied by highly odor-appropriate behavior, such as searching for a "gas leak." This is the only objective evidence we have for the presence of an OH. Third, where OHs occur repeatedly, the person may gain insight into the nature of these experiences, although this may depend upon whether there is an underlying psychopathology (e.g., insight appears more common in epileptic than in schizophrenic OHs).

There are two other features that warrant comment. The first is the perceived locus of the OH. This can be in the nose or mouth, on the surface of the body or in the external environment. A defining feature (more below) of some forms of OH is their location, notably in olfactory reference syndrome, in which a person is convinced that their own body emanates a foul smell. In these cases, the person may not in fact be hallucinating a smell, rather the person infers the presence of a smell from other peoples reaction to them.

Presentation

Healthy Adults

Olfactory hallucinations (OHs) are widely reported in healthy adults. A large study of the frequency of all types of hallucination, conducted in Western Europe, revealed that 8.6% of the sample had experienced an OH, and that 0.9% of the sample experienced these several times a week [2]. OHs were the commonest reported daytime hallucination across all modalities. Other studies of non-clinical populations have found that OHs occur more frequently in individuals scoring higher on measures of psychosis-proneness.

Primary Symptom

OHs can occur as a sole presenting symptom in the condition termed phantosmia. The prevalence of phantosmia is unknown, but according to Leopold [3] it occurs more frequently in women, and is a progressively worsening, relapsing and remitting condition, with lifelong duration. Whilst OHs may be brief, phantosmia may be considerably more persistent, in some cases the hallucination may last hours or days, nonetheless even with this different time-course, it still fulfils the general definition of an OH.

Secondary Symptom

Schizophrenia: With the exception of epilepsy (more below), OHs have been studied most extensively in schizophrenia. An early view was that the presence of OHs was indicative of a poor prognosis, but there does not appear to be any substantial support for this notion. Rather, OHs appear to co-occur with tactile hallucinations and other positive symptoms of the disease. Phenomenologically, schizophrenic OHs are qualitatively varied, but may occasionally include descriptions, which suggest a delusion rather than an OH (e.g., smell of aliens, devils breath and angels). In most cases the OHs are reported as unpleasant or disgusting. Prevalence estimates vary between 2–35%. Most OHs are attributed to an external source (with some notable exceptions – see [4], for an excellent and representative set of examples), are of a similar time-course to real olfactory experiences and can result in behaviors consistent with the OH (e.g., escaping a building smelling of smoke).

Epilepsy: OHs can occur in the hours or days before a seizure (prodromal) or immediately, within minutes, preceding a seizure. These experiences are usually termed auras and estimates vary as to their prevalence (1–30%; [5]). Phenomenologically, these OHs cover all odor qualities, are brief, localized to the environment, and are predominantly unpleasant. An interesting feature is that they may be repetitive, in that the same person always experiences the same OH.

Migraine: OHs can occur prior to a migraine (again described as auras), with the same time course and features (immediate vs. prodromal) as in Epilepsy.

Post-traumatic stress disorder (PTSD): Several papers have documented OHs in PTSD under circumstances where the person is re-exposed (or imagines) to contextual cues associated with the event (e.g., smelling smoke/gasoline whilst traveling in a car following a traumatic motor vehicle accident). In all cases, the OH appears specific and appropriate to the traumatic event.

Brain injury: Both traumatic brain injury, stroke and aneurysm can result in OHs. In some cases these more

closely resemble phantosmia (and may share similar causation via damage to peripheral olfactory structures) whilst in others, especially aneurysm and stroke, the OHs may be complex (integrated) and hedonically varied.

Drug abuse: OHs have been reported in both chronic cocaine and alcohol users, but studies are few and so prevalence cannot be estimated. These reports indicate a presentation akin to that observed in Epilepsy – predominantly negative, brief and qualitatively varied OHs.

Miscellaneous: OHs have also been described, albeit rarely, in Parkinson's disease, Charles Bonnet syndrome, Depression and Alzheimer's disease.

Cause

Whilst there has been fairly long history of theoretical and empirical work on visual and auditory hallucinations, especially in schizophrenia, relatively little work has been undertaken in respect to olfactory hallucinations (OH). This section starts by examining the association between the olfactory system and the two clinical conditions in which OHs are most well documented (epilepsy and schizophrenia), and then outlines theories that may account for OHs in these conditions. The second part of this section examines phantosmia, and the final part OHs in normal participants.

Epilepsy and Schizophrenia

The neural basis of epilepsy and schizophrenia can overlap with brain areas known to be involved in olfactory function. In epilepsy, olfactory abnormalities tend only to accompany the disorder when the focus for the seizure is in the temporal lobe. Here the seizure may start or propagate to the amygdala and uncus and then into primary olfactory processing areas located on the boundary of the frontal and temporal lobes. Not surprisingly then, OHs (auras) tend to be associated with temporal lobe epilepsy. In schizophrenia, abnormalities have been detected in the orbito frontal cortex (OFC), amygdala and medio-dorsal nucleus of the thalamus (MDNT). Respectively, the OFC is secondary olfactory cortex, the amygdala is involved in processing the hedonic valence of odors and the MDNT is one of the routes by which information flows from primary olfactory cortex to secondary olfactory cortex, and may be instrumental in attributing the source of sensory stimulation ("that's a smell").

There are several contemporary theories of hallucinations [6], including cortical irritation, cortical release, intrusion of imagery or dreams, and attentional/sensory impairment theories. How well do these models account for OHs in epilepsy and schizophrenia? Cortical irritation is the oldest hypothesis and suggests that excess neural activity at a particular brain loci results in the activation of memory traces that are then experienced as real events. Whilst this was heavily based on electrical brain stimulation (EBS) studies, it turns out that EBS results in *very few* olfactory-related experiences. This conclusion is based upon a large number of reported studies, stimulating many regions in the temporal/frontal regions. The rarity of these events suggests that focal irritation in brain areas known to be abnormal, especially in temporal lobe epilepsy, is an unlikely explanation.

A second class of explanation (of varying form) is that hallucinations arise as a result of abnormal – typically reduced – sensory input. This results in cortical release or hyperexcitability, causing memories of prior sensory experience to be re-experienced as real. There is one major problem with this account for OHs in epilepsy and schizophrenia. This is that patients who experience OHs may not have reduced sensory input. Three studies have examined schizophrenic participants with OHs. They find no consistent deficit in ►odor detection, no abnormal changes to olfactory mucosa, and no history of disease states that might affect olfactory function. With epilepsy, the picture is less clear, with no systematic studies as yet. However, olfactory deficits in temporal lobe epilepsy are usually indicative of central (i.e., ►odor identification and ►odor discrimination) rather than peripheral pathology (i.e., detection is typically intact). Thus there is likely to be no reduction of sensory input that this class of theory would require.

The third class of explanation suggests that hallucinations result from the intrusion of dreams into the waking state or the misattribution of imagery to the external environment, rather than correctly to oneself. Whilst both of these types of explanation have been extensively explored, especially in respect to auditory hallucinations of people conversing, they have significant obstacles to overcome as an account of OHs. Whilst olfactory dreams and images certainly do occur, the former are rare and the latter are hard to generate [7]. Indeed, some argue that we may have no capacity to consciously experience odor images at all. In this case, misattribution accounts may not have much utility in explaining OHs.

A further, and more recent class of model suggests that hallucinations arise from a combination of attentional deficits and impaired sensory functioning. As noted above, impaired sensory functioning (detection) does not appear to be a salient feature of either epilepsy or schizophrenia.

Finally, there are a number of other possible causes of OHs in epilepsy and schizophrenia that have not been widely canvassed. First, impaired odor identification might lead to what *appears* to be an OH (e.g., misidentifying the smell of table polish for smoke). Second, the likely presence of amygdala abnormalities in schizophrenia and epilepsy, the predominantly unpleasant nature of OHs and the amygdala's role in mediating aversive reactions to odors, might suggest

this as a possible neural locus for these events. In summary, there is at present no well-defined model of OHs and there is a need to test the various theoretical accounts described above more directly.

Phantosmia

Whilst epileptic and schizophrenic OHs likely involve a dominant central cause, phantosmia almost certainly derives from a combination of both peripheral and central causes [3]. Evidence favoring a peripheral basis for phantosmia is that it typically disappears if the olfactory mucosa is treated with a local anesthetic and that examination of excised mucosal tissue from phantosmia patients reveals disordered axon growth and an abnormal ratio of mature to immature neurons. Evidence favoring a central locus comes from the finding that many phantosmia patients have no detectable abnormality in odor detection and that such patients typically have no history of upper respiratory tract infection or head injury prior to onset. Interestingly, magnetic resonance spectroscopy imagining has revealed significantly lowered GABA levels in several central sites, including the amygdala [8]. Given the overwhelming predominance of unpleasant OHs in phantosmia, this again suggests possible amygdala pathology as a common feature of OHs.

Normal Participants

Several studies suggest that OHs are more common in healthy individuals who score higher on measures of schizotpy or psychosis-like dimensions, although it is not currently possible to estimate the proportion of variance accounted for by this variable [9]. What it does suggest, however, is that normal variation in schizotypy may reflect proneness to OHs, implying a similar causal explanation to those described above for schizophrenia. In addition, a proportion of OH-like experiences may also be accounted for by more mundane failures to identify an odor source, misperceptions (which may be more common in olfaction than in other senses), illicit drug use, alcohol, anxiety and depression, and lack of sleep [2].

Conclusion

The study of hallucinations can offer important insights into clinical conditions such as schizophrenia, as well as revealing much about routine perceptual processing. The study of OHs is not well advanced, empirically or theoretically, but it will be important in testing the generality of current theories of hallucinations.

References

1. Greenberg MS (1992) Olfactory hallucinations. In: Serby MJ, Chobor KL (eds) Science of olfaction. Springer, New York, pp 467–499
2. Ohayon MM (2000) Prevalence of hallucinations and their pathological associations in the general population. Psychiatry Res 97:153–164
3. Leopold D (2002) Distortion of olfactory perception: diagnosis and treatment. Chem Senses 27:611–615
4. Bromberg W, Schilder P (1934) Olfactory imagination and olfactory hallucinations. Arch Neurol Psychiatry 32:467–492
5. West SE, Doty RL (1995) Influence of epilepsy and temporal lobe resection on olfactory function. Epilepsia 36:531–542
6. Collerton D, Perry E, McKeith I (2005) Why people see things that are not there: a novel perception and attention deficit model for recurrent complex visual hallucinations. Behav Brain Sci 28:737–794
7. Stevenson RJ, Case TI (2005) Olfactory imagery: a review. Psychon Bull Rev 12:244–264
8. Levy LM, Henkin RI (2004) Brain GABA levels are decreased in patients with phantageusia and phantosmia demonstrated by magnetic resonance spectroscopy. J Comput Assist Tomogr 28:721–727
9. Bell V, Halligan PW, Ellis HD (2006) The Cardiff Anomalous Perceptions Scale (CAPS): a new validated measure of anomalous perceptual experience. Schizophrenia Bulletin 32:366–377

Olfactory Information

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Synonyms

Odors; Odorants; Odor code; Olfactory system dynamics

Definition

Olfactory information can refer to the chemical stimuli (odorants), the perceptual effect of the stimuli (odors), the individual neural responses which receive this input (odor code), and the dynamical interaction of the many brain subsystems which comprise the central olfactory pathways (olfactory system dynamics).

Characteristics

►Odor signals can be viewed as stereotyped activation maps defined by neuronal ►receptive fields and also as perceptual objects in which the odorant stimuli are associated with meaning, behavior and experience. The anatomy and physiology of the mammalian olfactory system has been studied from both perspectives. The ►olfactory bulb receives direct input from ►olfactory receptor neurons in the olfactory epithelium. These neurons project in a "receptor-topic" arrangement, such

that an individual ►glomerulus receives input from only one type of receptor (Fig. 1).

Because an individual odorant can activate multiple ►olfactory receptors, glomerular input maps are fragmented and highly distributed representations in the form of glomerular activation patterns. The patterns also have a dynamic structure which can be seen using ►Ca^{++} imaging.

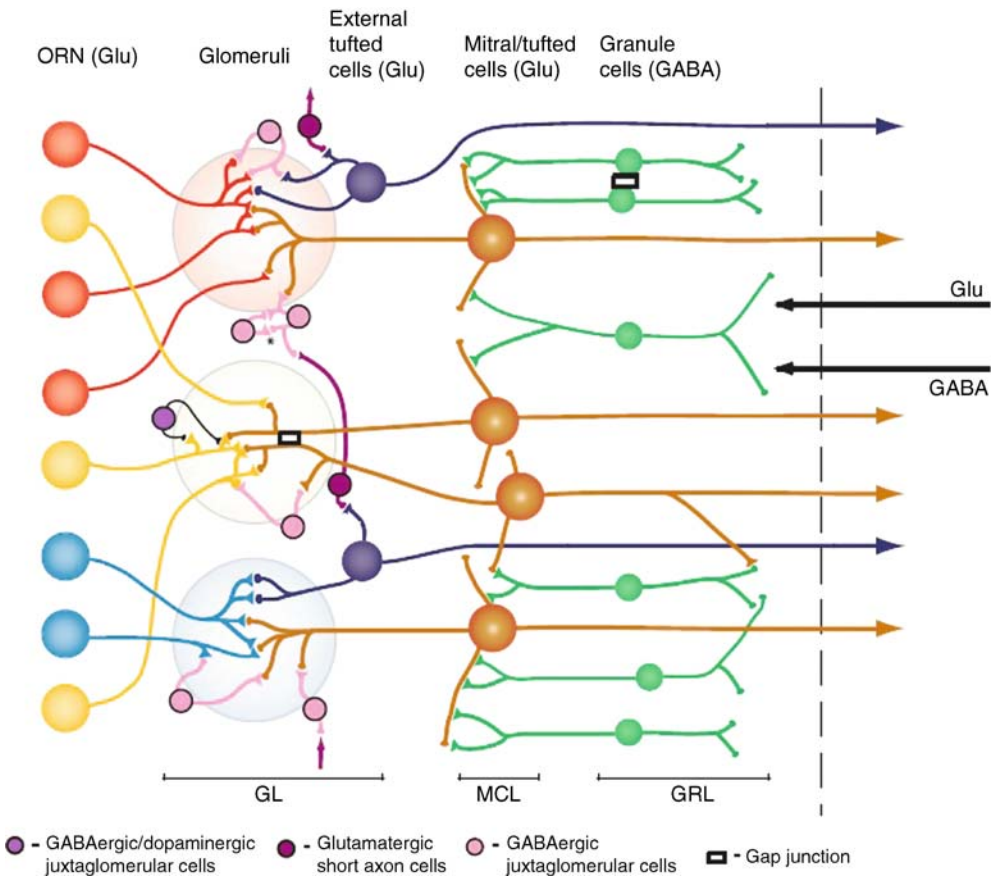
The mammalian ►olfactory system is also characterized by dense bidirectional connectivity among its many structures. The ►olfactory bulb may receive more synaptic input from the brain than it does from the olfactory receptor sheet, similar to a comparison of retinal and V1 projections to the thalamic ►lateral geniculate nucleus. Olfactory bulb structure has been likened at different times to the ►retina, primary visual cortex and more recently the sensory ►thalamus [2]. This essay concentrates on the mammalian system, but some references to the analogous insect systems are made [1]. The peripheral input structure, glomerular architecture and ►centrifugal input all have perceptual and physiological consequences.

Odor Psychophysics in Animals

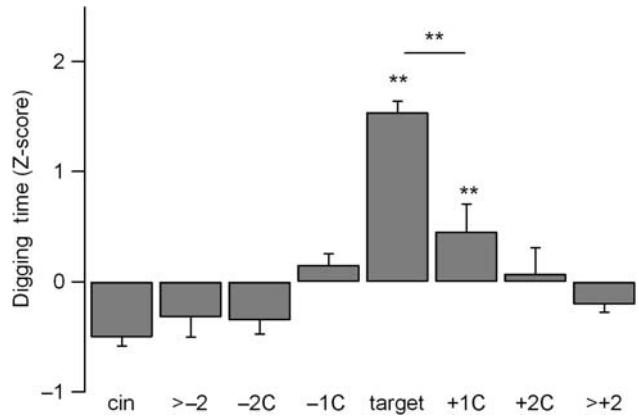
Psychophysical studies examining odor similarity use generalization methods, in which animals are trained to recognize one odorant, and similarities are judged by generalization of a behavioral response to other odors. Taking the ►glomerular input maps produced by various imaging methods and ►mitral cell responses corresponding to these areas as a guide, many compounds have been shown to exhibit similarity gradients along changes in molecular features, such as carbon chain length [3].

Thus, there are similarities in chemical composition, receptor activation and input patterns, which then correspond to similarities in odor quality. On the other hand, most animals are also very good at distinguishing even very similar odorants, and ►reinforcement learning can help an individual to discern even very small differences in glomerular activation patterns (Fig. 2).

Psychophysical responses to monomolecular odorants are relatively stable over a range of concentrations, due in part to mechanisms within the input layer. A subpopulation of ►GABAergic periglomerular cells



Olfactory Information. Figure 1 Schematic of olfactory bulb architecture. GL – glomerular layer; MCL – mitral cell layer; GRL – granule cell layer. Pial surface on the *left*, centrifugal inputs on the *right* (Reprinted from [1] with permission; Elsevier).



Olfactory Information. Figure 2 Example of carbon chain length generalization pattern for a series of aldehydes. Mice trained to dig in cage bedding scented with a single aliphatic aldehyde (target) generalize the response to a nearby aldehyde (1 carbon difference in chain length). Digging times are compared to other aldehydes of chain lengths longer and shorter than the target and a control odor (cin – cineole).

receives direct input from the ►olfactory nerve and mediates feedforward inhibition onto the ►mitral cell apical dendrites. Release of ►dopamine by ►juxtaglomerular cells and ►acetylcholine by the horizontal nucleus of the diagonal band of Broca in the ►cholinergic basal forebrain also modulate the incoming ►afferent activity. ►Excitatory and ►inhibitory connections among glomeruli and lateral inhibition between mitral and granule cells have been proposed as mechanisms for ►contrast enhancement and ►gain control.

Odor mixtures present a more complex picture, and two behavioral methods have been used to investigate their perceptual properties in animals. The first looks at mixture quality, in which ►associative learning or ►habituation is used to train an animal to recognize a given mixture, and components are then tested in a ►generalization paradigm. These studies suggest a general theoretical principle: odors that smell alike or activate significantly overlapping receptor or glomerular populations produce a ►synthetic or ►configural (►Configural/Configurational) quality. Mixtures of dissimilar or nonoverlapping odors produce ►elemental qualities. However, there is growing evidence that mixture perception may not be so simple, as compounds with similar structures can produce elemental responses, and those with very different structures can produce synthetic responses in binary mixtures. Furthermore, as the number of compounds in a mixture grows, humans experience more synthetic effects. Concentration and pungency also significantly affect mixture perception.

The second method of assessing mixture perception addresses animals' ability to recognize the ratio of various odor components, in which they choose a response associated with the component represented at higher concentration [4]. Responses in this case follow a ►psychometric curve (►Psychometric Curve/Psychometric Function). This method does not specifically address odor mixture quality, but it can be used to manipulate odor discrimination difficulty. What this method has been able to show is that rodents can identify some odors in 1–2 sniffs, but as discrimination becomes more difficult this brief sampling time results in poorer performance. Training rats to sniff longer results in greater performance levels in more difficult discriminations; this suggests a ►speed-accuracy tradeoff in odor sampling.

The mechanisms for learning differences between odors in a behavioral context involve areas of the brain beyond the ►glomerular maps and are addressed at the physiological level.

Physiology of Olfactory Information

Ease of access to the olfactory bulb and the importance of olfactory information for rodents drove this research to very deep levels even before single unit recordings in waking and mobile animals became technically feasible or practical. Thus, this field proceeded from its beginning at the systems level, only more recently addressing issues such as ►odor coding and ►receptive fields. However, because of the high-dimensional nature of olfactory stimuli, we still know relatively little about the relative importance of salient molecular features, concentration, ►pungency or even the existence of odor ►categories. (Much of the anatomical, physiological and computational background is reviewed in a few sources [1,5,6].)

Individual Neuron Responses

►Mitral cells in the ►olfactory bulb typically respond in a ►burst-like manner around the peak of inhalation. They receive input from a single ►glomerulus, and

those with dendrites in the same glomerulus can excite each other. In anesthetized mammals, mitral and ►tufted cells in the ►olfactory bulb and ►pyramidal cells in the ►piriform cortex can respond with an increase or decrease in firing rate upon presentation of odorants in front of an animal's nose. In this situation mitral cells show relatively stable odor responses that correspond roughly to the ordered representations suggested by mapping studies. However, there are exceptions to this simple ordering, since many mitral cells respond to many different odor classes, and in any given place in the olfactory bulb, one can often find cells that respond to an odor class.

Mitral and tufted cells in the olfactory bulb respond in a graded fashion to similar odorants, reminiscent of classical ►receptive fields with broad ►tuning curves that can be shifted by prolonged exposure to non-optimal odorants within a cell's ►receptive field. This plasticity is similar to that in other sensory systems, such as receptive field ►learning-induced plasticity in ►auditory cortex. Mitral cells show significant cross-habituation to odors within their receptive fields. Odor responses of pyramidal cells in piriform cortex of anesthetized rats are somewhat different. While these cells exhibit tuning curve properties similar to mitral cells, the responses of single neurons to related odorants do not cross-habituate, suggesting that odor responses within the piriform cortex are more selective overall than those within the olfactory bulb.

Waking mammals present a somewhat different picture. ►Odor selectivity has been recorded in a handful of studies, limited by the difficulty of recording isolated mitral cells in waking mammals. The phase of the respiratory cycle in which a mitral cell fires during periods of slow breathing (< 5 Hz in rats) represents the identity of a relatively long (5 s) odor stimulus associated with reinforcement. However, when rats perform odor discriminations with a briefer sampling time (1–2 s), they sniff at high rates (6–12 Hz), and mitral cells uncouple from the respiratory cycle. Firing rate responses in waking rats predict behavior most strongly, and only a small part of a cell's response varies with odor. When the behavioral association (positive or negative reinforcement) of an odor is changed, a cell's odor selectivity also changes. Studies of single neuron firing patterns in the ►piriform cortex of waking mammals are scarce, but odor responses there are also modified by changes in behavioral associations.

Population Activity

Population physiology presents a window into system-level dynamics. The ►local field potential has been very useful for understanding how the various parts of the olfactory and limbic systems interact with and control each other. Many early studies described the parameters which govern oscillatory responses in many parts of the olfactory system and those which relate local field potentials to single neuron activity [7,8]. The olfactory bulb exhibits two major classes of oscillations, slow (< 12 Hz) and fast (>12 Hz) (Fig. 3).

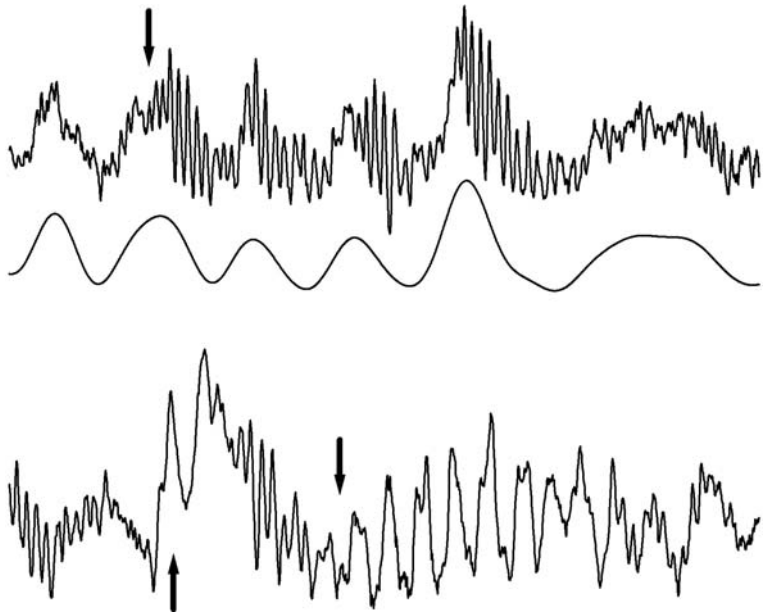
Slow Temporal Structure

Slow oscillations are in the ►theta frequency range (2–12 Hz in the olfactory bulb) for rodents and are generally correlated in phase and frequency with the respiratory cycle and with mitral cell burst firing. They are supported by afferent input and by intrinsically bursting cells like the ►external tufted cells in the ►glomerular layer. The burst behavior of mitral cells leads to a loose temporal structure within the olfactory bulb, in which within a 100–150 ms time window many cells are activated, and in the exhalation phase and prior to the next inhalation fewer cells are activated. Thus, the ►theta oscillation in the olfactory bulb represents these high and low firing states. At low respiratory rates, this leads to a sampling of the olfactory environment in the nose approximately every 300 ms in a ►saccade-like fashion. However, respiration does not completely describe these rhythms or mitral cells' firing patterns even in anesthetized animals, and there is evidence that ►centrifugal inputs can modulate both. During fast sniffing, mitral cells tend to fire ►tonically and the theta rhythm no longer represents high and low firing rates in the mitral cell population. Also during fast sniffing coupling between the hippocampal theta rhythm and sniffing or olfactory bulb oscillations in the high theta range (>5 Hz) have been associated with learning and performance of odor discriminations. Otherwise, these two rhythms are uncorrelated. This low frequency coupling may aid information transfer between the olfactory and hippocampal systems.

Fast Temporal Structure: Circuit Properties

Within the respiratory cycle there is structure at a finer timescale. At the end of inhalation the ►gamma oscillation (~40–100 Hz) is initiated. This odor-evoked oscillation was first described by Adrian [9]. The gamma burst lasts for 60–100 ms at low respiratory rates (~6–8 cycles per burst; Fig. 3). These fast odor-evoked oscillations have been well-studied at the physiological and computational levels in this system and in the analogous insect system [5]. Most researchers agree that olfactory bulb gamma oscillations arise from the reciprocal dendrodendritic (►Reciprocal Dendro-dendritic Synapse) interaction between mitral and granule cells in the ►external plexiform layer in a ►negative feedback circuit. Olfactory bulb mitral cells' firing times are probabilistically related to the popula-tion-level gamma oscillation (Fig. 4).

While this oscillation is often referred to as a source of ►synchrony between individual neurons, it more



Olfactory Information. Figure 3 Olfactory bulb oscillations (local field potential; each trace is 1 s long). *Top* trace shows gamma oscillations initiated at the peak of inhalation (*downward arrow*). The ►theta band part of the signal is shown just below, with each cycle representing a sniff. *Bottom* trace shows an odor-evoked beta oscillation. *Upward arrow* is the ►sensory evoked potential, and *downward arrow* shows the onset of the ►beta oscillation.

precisely represents the level of synchrony between individual neurons and the ►emergent local field potential. In this case, an increase in gamma oscillation power and a decrease in spectral width are associated with mitral cells firing in more restricted time windows, rather than precise temporal synchrony between neurons. This suggests increased precision in the temporal structure of the olfactory information.

Odor-evoked oscillations also occur in the insect ►antennal lobe, which is an analogue of the olfactory bulb, with very similar circuit properties. While insect oscillations are ~20 Hz, they are similar to mammalian gamma oscillations in the relationship of the principal neurons' firing patterns to the oscillatory local field potential and the dependence of the oscillations on the interaction between excitatory ►projection neurons and the ►GABAergic local neurons. In the insect system it has been shown that a group of projection neurons fires in an odor-specific temporal pattern across cycles of the fast oscillations [1], which has led some to conclude that the mammalian system may use a similar mechanism during periods of high amplitude gamma oscillations.

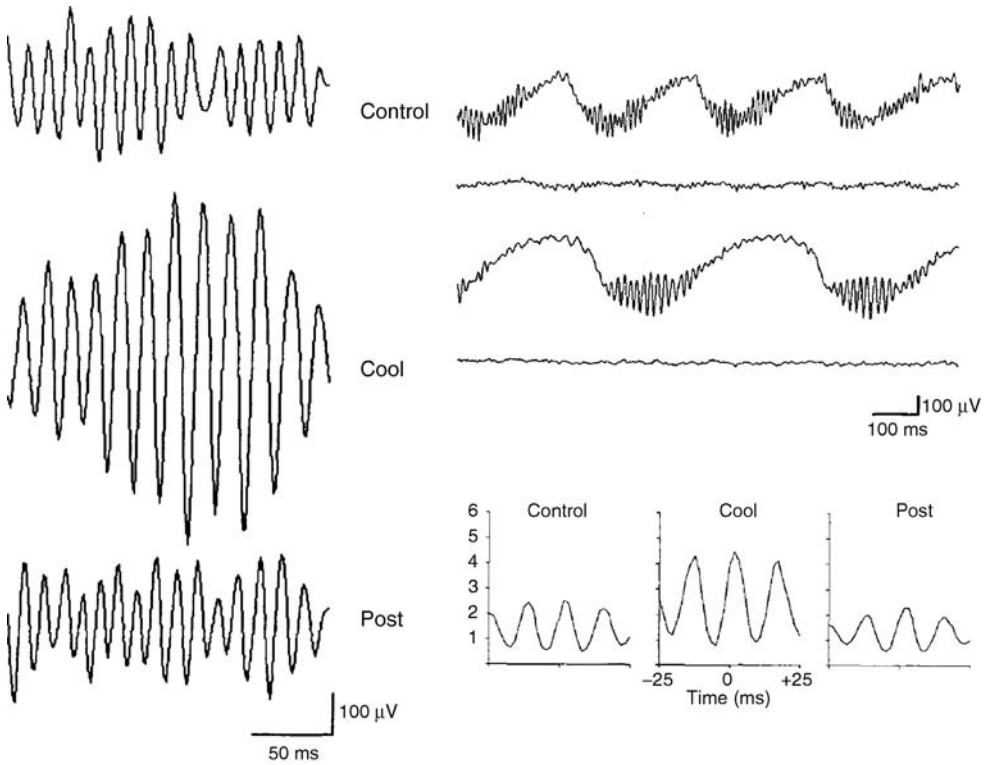
In the mammalian system, sources of ►desynchronization of the local field potential associated with this system lie in the centrifugal and intrabulbar sources of drive to the ►granule cell layer, both ►GABAergic and ►glutamatergic (Fig. 4). Desynchronization is seen as a source of stability and flexibility in this system, and may be important for understanding the functional differences between the mammalian systems and the simpler insect system.

In waking rats and mice, the gamma band has been further subdivided into two bands that are distinct in their behavioral associations but sometimes overlap in frequency. Gamma 1 (~70 Hz in waking rats and mice) is used to refer to the classical odor-evoked gamma described above. Gamma 2 (~55 Hz) is used to refer to the somewhat lower frequency oscillation that occurs between breaths during periods of alert immobility and low breathing rates. The source of gamma 2 oscillations is different from that of gamma 1, likely arising from ►GABAergic drive to the granule cells. The functional association of these oscillations is unknown, but may be related to attentional processes or dynamic stability.

Fast Temporal Structure: Perceptual Properties

Activity in the ►gamma frequency band has been associated with odor discrimination circuitry in many species. Walter J. Freeman and colleagues showed that over the surface of the olfactory bulb there is a common ►gamma band waveform of the ►EEG [10]. The spatial patterns of amplitude of this waveform were the best indicator of an odor, and the patterns were produced reliably only when meaning (positive or negative reinforcement) was associated with an odor.

Gamma band (and gamma-like) oscillatory population synchrony is one specific mechanism associated with more difficult or highly overlapping odor discriminations



Olfactory Information. Figure 4 Centrifugal input to the olfactory bulb causes desynchronization of the local field potential. Cooling the rear portion of the olfactory bulb effectively blocks input from the rest of the brain and produces a large increase in ►gamma oscillation power. Pulse probability density (*bottom traces*) shows that single mitral cells are more strongly coupled with the local field potential gamma oscillation without centrifugal input (Compiled and reprinted with permission from Springer, Gray and Skinner, *Exp Brain Res* 1988. 69(2):378–386.).

in rodents and insects. Disruption of these oscillations in honeybees leads to a selective decrease in discriminating highly overlapping odorants (fine discrimination). Increased olfactory bulb gamma power in β3 knockout mice leads to a selective increase in fine odor discrimination. In both studies, coarse discrimination was unaffected. Unmanipulated rats dramatically increase the power of gamma oscillations when performing fine odor discrimination, relative to coarse discrimination in a two-alternative choice task, suggesting that temporal precision in mitral cell firing patterns is enhanced.

Odor-associated beta band oscillations (15–30 Hz) are also seen in waking rats, where they predict the onset of correct performance in Go/No-Go odor discrimination tasks. Beta oscillations occur concurrently in the ►olfactory bulb, ►piriform cortex, ►entorhinal cortex, and dorsal and ventral ►hippocampus. Similar oscillations occur in the olfactory bulb, piriform cortex, entorhinal cortex and hippocampus during repeated passive odor stimulation in a ►sensitization-like fashion (Fig. 3). Beta oscillations differ significantly from gamma oscillations in that they require a complete bidirectional loop between the olfactory bulb and the rest of the olfactory system, suggesting temporal structure distributed across many brain areas. In anesthetized rats, beta oscillations occur at the end of exhalation, and this period has been associated with enhanced firing in the granule cell layer.

Summary

The combination of ordered but highly complex input maps combines with centrifugal input to the olfactory bulb and oscillatory dynamical states to produce odor perception. Input pattern overlap predicts odor similarity and discrimination difficulty, and animals can adjust their sniffing behavior along with changes in the olfactory system to interpret and respond to odors. Fast oscillations represent cell assemblies that process odors within and between olfactory areas, and slow oscillations at the respiratory frequency can serve momentary system wide coupling possibly to facilitate information transfer.

References

1. Kay LM, Stopfer M (2006) Information processing in the olfactory systems of insects and vertebrates. Semin Cell Dev Biol 17(4):433–442
2. Kay LM, Sherman SM (2007) An argument for an olfactory thalamus. Trends Neurosci 30(2):47–53

3. Cleland TA et al (2002) Behavioral models of odor similarity. Behav Neurosci 116(2):222–231
4. Rinberg D, Koulakov A, Gelperin A (2006) Speed-accuracy tradeoff in olfaction. Neuron 51(3):351–358
5. Cleland TA, Linster C (2005) Computation in the olfactory system. Chem Senses, 30(9):801–813
6. Shipley MT, McLean JH, Ennis M (1995) Olfactory system. In: Paxinos G (ed) The rat nervous system. Academic Press, San Diego
7. Freeman WJ (1975) Mass action in the nervous system. Academic Press, New York, p 489
8. Rall W, Shepherd GM (1968) Theoretical reconstruction of field potentials and dendrodendritic synaptic interactions in olfactory bulb. J Neurophysiol, 31(6):884–915
9. Adrian ED (1942) Olfactory reactions in the brain of the hedgehog. J Physiol, 100:459–473
10. Freeman WJ, Schneider W (1982) Changes in spatial patterns of rabbit olfactory EEG with conditioning to odors. Psychophysiology 19(1):44–56

Olfactory Learning

►Odor – Memory
►Olfactory Plasticity

Olfactory Marker Protein

Definition

A cytoplasmic protein expressed at high levels ubiquitously and exclusively throughout the soma, cilia, and axon of olfactory sensory neurons. Its function remains obscure.

►Olfactory Sensory Neuron

Olfactory Nerve

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Synonyms

First cranial nerve; Olfactory sensory inputs

Definition

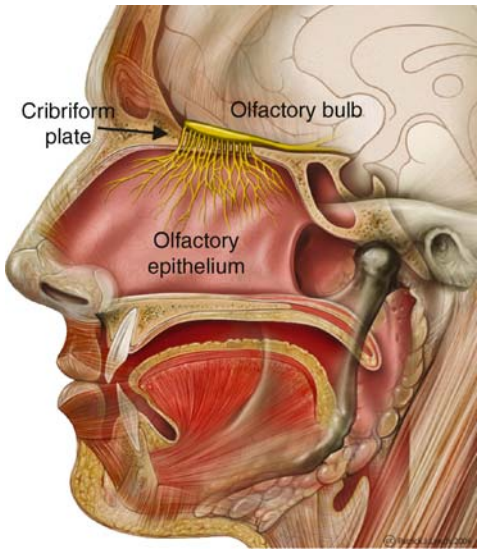
The olfactory nerve consists of the axonal projections of olfactory sensory neurons, which extend from the olfactory epithelium in the nose through the cribriform plate of the skull to contact postsynaptic targets in the glomeruli of the olfactory bulb. Uniquely among pathways in the central nervous system, the entire nerve is continuously regenerated throughout adult life and has a remarkable capacity for recovery from injury.

Characteristics

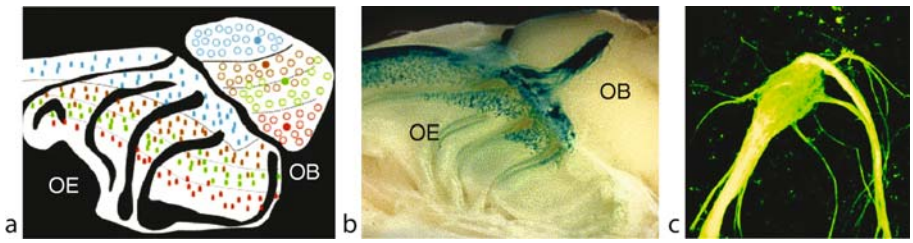
Anatomy, Morphology, and Molecular Characteristics

The olfactory nerve is the shortest of the cranial nerves, and is one of only two – along with the optic nerve – which do not project to the brainstem. It is composed primarily of the axons of olfactory sensory neurons (OSNs), which sit in the olfactory epithelium (OE) of the nasal cavity and whose job is to transduce information in airborne odorant molecules into electrical signals that are sent to the brain's olfactory bulb (OB). OSN axons are small (~0.2μm diameter) and unmyelinated, and extend from the OE into the underlying lamina propria of the olfactory mucosa, where they coalesce into small-sized bundles. These bundles increase in size as they exit the lamina propria, and form branches of the olfactory nerve that cross through perforations of the skull's cribriform plate before entering the outer nerve layer (ONL) of the OB (Fig. 1).

Having crossed the boundary between the peripheral and central nervous systems, OSN axons then exit the



Olfactory Nerve. Figure 1 Olfactory nerve. The axons of olfactory sensory neurons in the olfactory epithelium, shown here in yellow, project through the cribriform plate of the skull to the olfactory bulb, also shown in yellow. Illustration © PJ Lynch and CC Jaffe.



Olfactory Nerve. Figure 2 Organization of olfactory nerve inputs to the olfactory bulb. (a) Zones in the olfactory epithelium (OE) project to particular regions of the olfactory bulb (OB). (b) Axons from olfactory sensory neurons that express a single type of olfactory receptor, labeled here in blue, project onto a single glomerulus in the medial OB. (c) Inputs to a single glomerulus are untidy, with axons entering the structure from all angles. (a) and (b) reprinted with permission from [1], (c) reprinted with permission from [2].

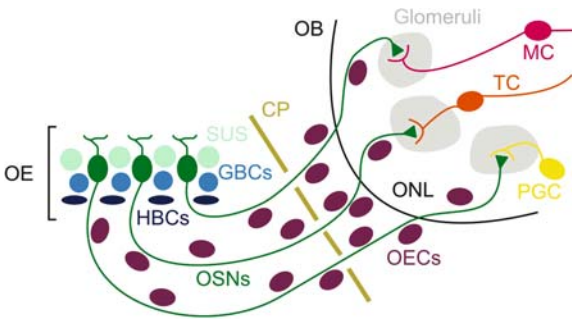
ONL to terminate in OB glomeruli (►Olfactory bulb glomeruli), specialized and highly complex arrangements of axons and ►dendrites that host the very first steps in odor information processing.

The organization of axons within the olfactory nerve is based on the olfactory receptor (OR) molecules expressed by OSNs. Each OSN expresses a single OR, and OSNs that express a particular OR lay scattered randomly within one of four OE zones. Each zone provides OSN axons that project to a particular region of the OB, although while the dorsal zone of the OE projects exclusively to the anterior dorsal bulb, the projections from other OE zones overlap somewhat [1] (Fig. 2a).

More striking is the astonishingly precise projection of OSN axons onto individual glomeruli: all of the OSNs expressing a given OR project onto only 2, mirror-symmetric glomeruli per bulb, and each glomerulus receives input only from axons expressing a single OR [1,3] (Fig. 2b). This huge OR-specific convergence only begins when the olfactory nerve reaches the ONL. Up to this point, axons from OSNs expressing different ORs are all completely intermingled, but on entry to the OB they begin a process of ►homotypic fasciculation whereby axons from OSNs with the same OR run together in bundles. These bundles then converge onto individual glomeruli, a highly specific process which is nonetheless surprisingly untidy [2] (Fig. 2c).

Once in the correct glomerulus, OSN axons make glutamatergic, excitatory synaptic connections with the dendrites of three main types of OB neuron (Fig. 3). Mitral cells (►Olfactory bulb mitral cells) and ►tufted cells are glumatergic projection neurons that receive olfactory nerve input and project directly to olfactory cortex. ►Periglomerular cells, in contrast, constitute a heterogeneous population of local interneurons that receive olfactory nerve input and make modulatory connections within and between glomeruli.

Along their route from OE to OB, OSN axons are surrounded and supported by the processes of



Olfactory Nerve. Figure 3 Cell types associated with the olfactory nerve. *OE* olfactory epithelium; *OB* olfactory bulb; *ONL* outer nerve layer; *CP* cribriform plate; *SUS* sustentacular cells; *GBCs* globose basal cells; *HBCs* horizontal basal cells; *OSNs* olfactory sensory neurons; *OECs* olfactory ensheathing cells; *MC* mitral cell; *TC* tufted cell; *PGC* periglomerular cell.

►olfactory ensheathing cells (OECs), glia that are unique to the olfactory nerve and which possess characteristics of both Schwann cells and astrocytes [4] (Fig. 3). OECs do not provide proper Schwann cell-style myelination, but instead extend thin processes which each wrap up to 200 OSN axons, providing them with mechanical and metabolic support. In addition, it appears that OECs are essential for the growth-permitting environment of the olfactory nerve, expressing guidance cues and neurotrophic factors which allow new OSN axons to make their way to the OB. Indeed, OECs have been used successfully to promote axon outgrowth and repair in models of CNS injury [4].

As well as possessing unique glia, the olfactory nerve also contains unique axons. Adult OSN axonal compartments contain molecules that are not found in most other axons of the mature CNS. These include mRNA, which appears to be transported along OSN axons rather than locally translated, transcription

factors, and cytoskeletal proteins such as MAP5 and vimentin which are more commonly found in developing neuronal processes [5]. OSN axons also contain ►olfactory marker protein (OMP), a molecule expressed strongly, ubiquitously, and uniquely throughout the olfactory nerve, but whose function remains obscure. Along with the permissive environment created by OECs, these unique axonal features of the olfactory nerve may underlie, or at least reflect, its regenerative capacity (see Adult Neurogenesis below).

Development

The olfactory nerve is initially established in rather early prenatal development. In mice, the first OSN axons arrive in the brain around embryonic day (E) 12, having extended from the OE through a "migratory mass" that includes OEC progenitors and guidepost mesenchyme cells [1]. Just before entering the presumptive OB, growing OSN axons wait for a short time before entering the ONL and fasciculating with other axons expressing the same OR. Fasciculated bundles are then directed to the region of their appropriate target glomerulus by molecular guidance cues including semaphorins, ephrins, and surface carbohydrates [1], with axons reaching specific domains in the presumptive glomerular layer as early as E15.5. The precise direction of OSN axons to their appropriate glomeruli depends at least in part on the particular ORs they express: aberrant glomerular targeting results when OR expression is genetically altered in a subset of OSNs [1]. Spontaneous, but not sensory activity in OSNs also appears necessary for the correct initial formation of OB glomeruli [6,7].

By postnatal day (P) 0, glomeruli in the rostral OB are clearly formed, while it takes a further 2–3 days for those in the caudal OB to catch up. However, the development of the olfactory nerve does not end there: at this stage, many OSNs axons expressing a particular OR terminate in two or more glomeruli. Over the next month or so of postnatal maturation, these diffuse projections are pruned to produce a tight, single glomerular target structure in each half-bulb (Fig. 4), a process that is highly dependent upon olfactory sensory experience [7].

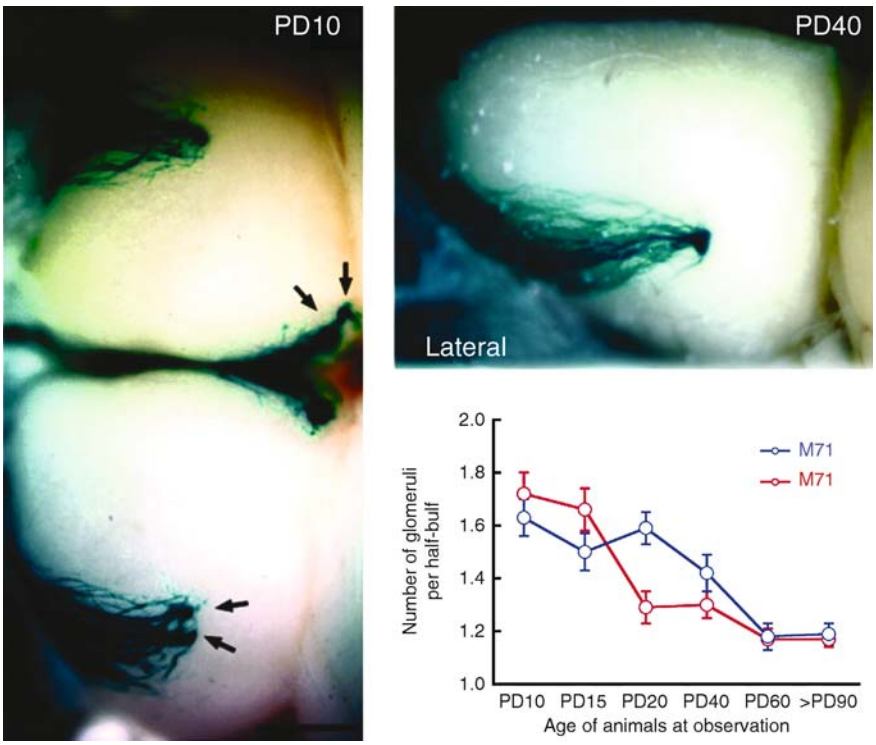
Adult Neurogenesis

The olfactory nerve is unique among CNS axon tracts in that its generative capacity extends past postnatal development and continues throughout adult life. Unlike other CNS neurons, the nature of OSNs' function as detectors of airborne odorants means they are directly exposed to the external environment, and thus to the accompanying risk of damage by toxins and pathogens. In order to maintain normal olfactory nerve function in the face of this threat, OSNs keep fresh by a process of continual turnover – after a lifetime of around 3 months, those that have not been killed already undergo programmed cell death and are replaced by new OSNs born from stem cells residing in the basal layer of the OE [8]. These cells migrate up to more superficial layers of the OE and extend an axon towards the OB, taking approximately 1 week post-mitosis to express mature markers such as OMP and to form functional glomerular synapses [8]. This normal replacement occurs with very high accuracy – there is no sign of degradation in the glomerular map with routine ageing. In addition, if a subpopulation of OSNs expressing the same OR is specifically removed, the replacement population extends axons to the OB and forms a glomerulus in precisely the right location. This entire process of OSN regeneration, and particularly the regrowth of olfactory nerve axons, probably involves many of the guidance factors and activity-dependent processes that orchestrate the initial formation of the olfactory nerve during brain development. In particular, OECs appear crucial to the growth-permissive status of the olfactory nerve environment throughout adult life.

The continual turnover of OSNs, and the presence of stem cells in the OE mean that the olfactory nerve is unique in the CNS in being able to recover from injury. After even drastic interventions such as section of the olfactory nerve or chemical lesion of the entire OE, recovery is possible – new OSN axons can extend and find the correct target zone of the OB after ~2–3 weeks [8]. There, recovery is not perfect: there are substantial targeting errors in an en-masse regenerating ON, producing multiple glomerular foci and incorrect terminal locations. However, although we currently know nothing about how the olfactory nerve functions following recovery from injury, we do know that olfactory behavior recovers extremely well. Whilst not anatomically perfect, then, the recovery capability of the olfactory nerve is easily good enough to restore useful olfactory function. Unsurprisingly, this unique ability has been the spur for many studies looking to use elements of the olfactory nerve niche to promote recovery in other models of CNS injury. Indeed, promising results have so far come from approaches involving ectopic transplantation of OECs.

Physiology and Function

The fundamental function of the olfactory nerve is to transmit olfactory information from its site of transduction in the OE to the site of its first processing in the glomeruli of the OB. This information is carried solely in the form of sodium-based action potentials, which are propagated along unmyelinated OSN axons at a speed of ~0.5m/s. Whether or not an action potential occurs in a given OSN axon depends on the particular OR expressed by the cell, and the presence of particular odorants in the olfactory environment. Individual OSNs are actually rather broadly-tuned

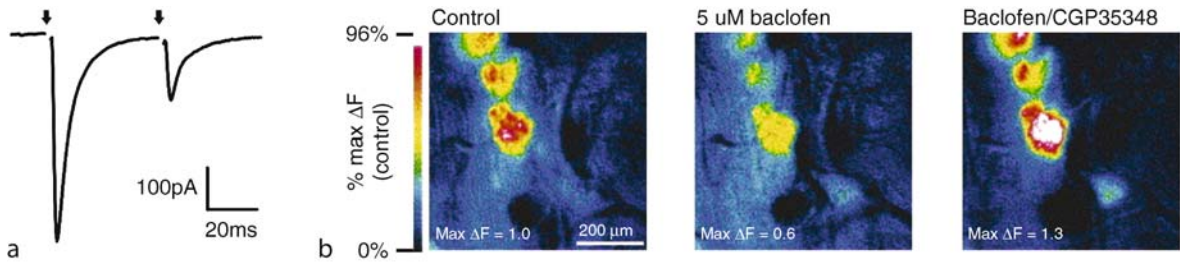


Olfactory Nerve. Figure 4 Postnatal refinement of olfactory nerve projections in mice. At postnatal day (PD) 10 (*left*), axons from olfactory sensory neurons expressing a single olfactory receptor type converge onto multiple glomeruli in the medial and lateral olfactory bulbs (arrows). By PD40 (*right*, *top*), axons converge onto a single glomerulus in the lateral bulb. The plot at bottom right shows the refinement of glomeruli with postnatal development for two distinct olfactory receptor types. Reprinted with permission from [7].

to odorants, since ORs can bind a relatively large number of different odorant molecules. Furthermore, even within a subgroup of OSNs that all express the same OR, variations in transduction processes mean that odorant responses can be markedly different. This means that the information carried by any one olfactory nerve axon actually says very little about which odorants are present or absent in the environment. Only a combinatorial code for odors, embedded in the activity of the ensemble of fibers constituting the olfactory nerve, can allow olfactory detection and discrimination to take place.

As well as the type of odorant stimulus present, the information carried by the olfactory nerve also depends on the strength of the activating odorants. As in all sensory systems, increasing the intensity of the stimulus produces an increase in firing frequency in olfactory nerve fibers. But this may not be the only temporal code present in the pathway, since different odorant concentrations are also known to evoke different firing *patterns* in olfactory nerve fibers. In addition, recordings of calcium activity in olfactory nerve axon terminals have revealed glomerulus-specific dynamics – some glomeruli are quicker, or longer-lasting than others. These differences in temporal dynamics are consistent for the same glomeruli across individual animals, and are only weakly correlated with odorant strength, suggesting they might represent another way, as well as firing frequency, that olfactory information is coded in the axons of individual OSNs.

Finally, coding in the axons of the olfactory nerve may be influenced by a rather unique process in the brain – ►ephaptic interactions between fibers. In most major axon tracts, firing in component axons is kept independent by myelination. The olfactory nerve, however, consists of bundles of hundreds of small axons loosely held together by the processes of OECs, meaning that the insulation of individual axons may not be very good. In these conditions, action potentials in one OSN axon could spread passively to activate other neighboring OSN axons. Indeed, mathematical models of the olfactory nerve suggest that such ephaptic interactions are possible, and even likely. Since OSN axons are not sorted by OR types until they reach the OB, these ephaptic effects could only act to disrupt OR-specific activity in particular fibers. If ephaptic interactions do occur in the real olfactory nerve, then, they may render the transmission of olfactory information from the nose to the brain far less than perfect.



Olfactory Nerve. Figure 5 Physiology of olfactory nerve terminals. (a) Evoked glutamatergic responses recorded in a periglomerular cell after paired stimulation of olfactory nerve inputs (arrows). Closely-spaced stimulation produces a depression of the second response, a feature characteristic of high release probability at olfactory nerve synapses. (b) Modulation of glutamate release at olfactory nerve synapses by $GABA_B$ receptors. Each blob shows release levels in an entire glomerulus in response to odorant stimulation. Release at olfactory nerve terminals is decreased by the $GABA_B$ receptor agonist baclofen, and increased by the $GABA_B$ receptor antagonist CGP35348. (a) recorded by the author, (b) reprinted with permission from [10].

In other sensory systems, primary sensory neurons transfer freshly-transduced electrical information about the world to their postsynaptic target cells via very reliable and morphologically specialized synaptic connections. In contrast, the connections of the olfactory nerve with its postsynaptic targets in OB glomeruli appear, structurally, to be rather normal glutamatergic synapses. However, functional experiments in OB slices have shown that these connections too are extremely reliable. Unusually for the brain, olfactory nerve terminals have very high release probability – ~0.8 or more [9] (Fig. 5a) which should ensure the highly reliable transfer of olfactory information from the OE to the brain. The underlying mechanisms subserving such high release probability are not known, although it is not due to multivesicular release, and the relationship between calcium entry and glutamate release appears to be nearly linear [9].

Whilst they transmit presynaptic activity with high fidelity, olfactory nerve terminals are unique among primary sensory afferents in being sites of extensive modulation. Although ultrastructural experiments have found no synapses *onto* olfactory nerve terminals in the OB, electrophysiological experiments have revealed strong modulation of release probability by GABA acting through $GABA_B$ receptors (Fig. 5b), by dopamine acting through D_2 receptors, and by cyclic nucleotides acting through terminally-expressed cyclic nucleotide-gated channels. This modulation is almost all intraglomerular, meaning that the immediate periglomerular cell postsynaptic targets of olfactory nerve terminals can release either GABA or dopamine, or both, to influence both their own inputs and others in the vicinity [10]. Such feedback modulation may ensure that, despite the high release probability at olfactory nerve synapses, the dynamic range of the terminals is maintained. In other words, the modulation ensures that the OB can still respond to a range of odorant concentrations, even after repeated or prolonged presentation of a strong stimulus.

References

1. Strotmann J, Breer H (2006) Formation of glomerular maps in the olfactory system. Semin Cell Dev Biol 17:402–410
2. Potter SM, Zheng C, Koos DS, Feinstein P, Fraser SE, Mombaerts P (2001) Structure and emergence of specific olfactory glomeruli in the mouse. J Neurosci 21:9713–9723
3. Treloar HB, Feinstein P, Mombaerts P, Greer CA (2002) Specificity of glomerular targeting by olfactory sensory axons. J Neurosci 22:2469–2477
4. Fairless R, Barnett SC (2005) Olfactory ensheathing cells: their role in central nervous system repair. Int J Biochem Cell Biol 37:693–699
5. Nedelec S, Dubacq C, Trembleau A (2005) Morphological and molecular features of the mammalian olfactory sensory neuron axons: what makes these axons so special? J Neurocytol 34:49–64
6. Yu CR, Power J, Barnea G, O' Donnell S, Brown HE, Osborne J, Axel R, Gogos JA (2004) Spontaneous neural activity is required for the establishment and maintenance of the olfactory sensory map. Neuron 42:553–566
7. Zou DJ, Feinstein P, Rivers AL, Mathews GA, Kim A, Greer CA, Mombaerts P, Firestein S (2004) Postnatal refinement of peripheral olfactory projections. Science 304:1976–1979
8. Schwob JE (2002) Neural regeneration and the peripheral olfactory system. Anat Rec 269:33–49
9. Murphy GJ, Glickfield LL, Balsen Z, Isaacson JS (2004) Sensory neuron signaling to the brain: properties of transmitter release from olfactory nerve terminals. J Neurosci 24:3023–3030
10. McGann JP, Pírez N, Gainey MA, Muratore C, Elias AS, Wachowiak M (2005) Odorant representations are modulated by intra- but not interglomerular presynaptic inhibition of olfactory sensory neurons. Neuron 48:1039–1053

Olfactory Pathways

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Synonyms

Olfactory structures; Olfactory cortical areas; Olfactory cortex

Definition

The perception of a smell is an integration of various sensations (olfactory, trigeminal, tactile, thermal, as well as gustatory sensations). This article is engaged with the olfactory pathways in particular. The human olfactory pathways can be divided into three parts [1,2] (Fig. 1):

(1) The olfactory receptors are located in the mucosa of the nasal cavities. From there olfactory nerves run to the olfactory bulb which is located inside the bony skull beneath the orbital forebrain. From an evolutionary point of view the olfactory bulb is not a ganglion but a part of the telencephalon, one of the oldest portions of the brain. Following this it is postulated that the olfactory bulb constitutes the genuine primary olfactory cortex [3], which is contradictory to the common literature.
(2) The olfactory tract connects the olfactory bulb to secondary olfactory cortex consisting of the anterior olfactory nucleus, the ►olfactory tubercle, the piriform cortex, parts of the amygdala (►peri-amygdaloid cortex, anterior and posterior cortical nuclei, nucleus of the lateral olfactory tract) and a small anteriomedial part of the entorhinal cortex. Since the recognition of the olfactory bulb as a cortical structure these areas are called secondary olfactory cortex [3].
(3) Regions known to receive projections from the secondary olfactory cortex include the orbitofrontal cortex, agranular insular cortex, additional subnuclei of the amygdala, medial and lateral hypothalamus, medial thalamus, basal ganglia, and hippocampus. These regions are termed tertiary olfactory regions.

Although the current understanding of the organization of the olfactory pathways depends basically on observations made in rodents and non-human primates, it is generally assumed that the human olfactory system owns the same basic organization.

Characteristics

Olfactory nerves/Primary Olfactory Cortex (POC)

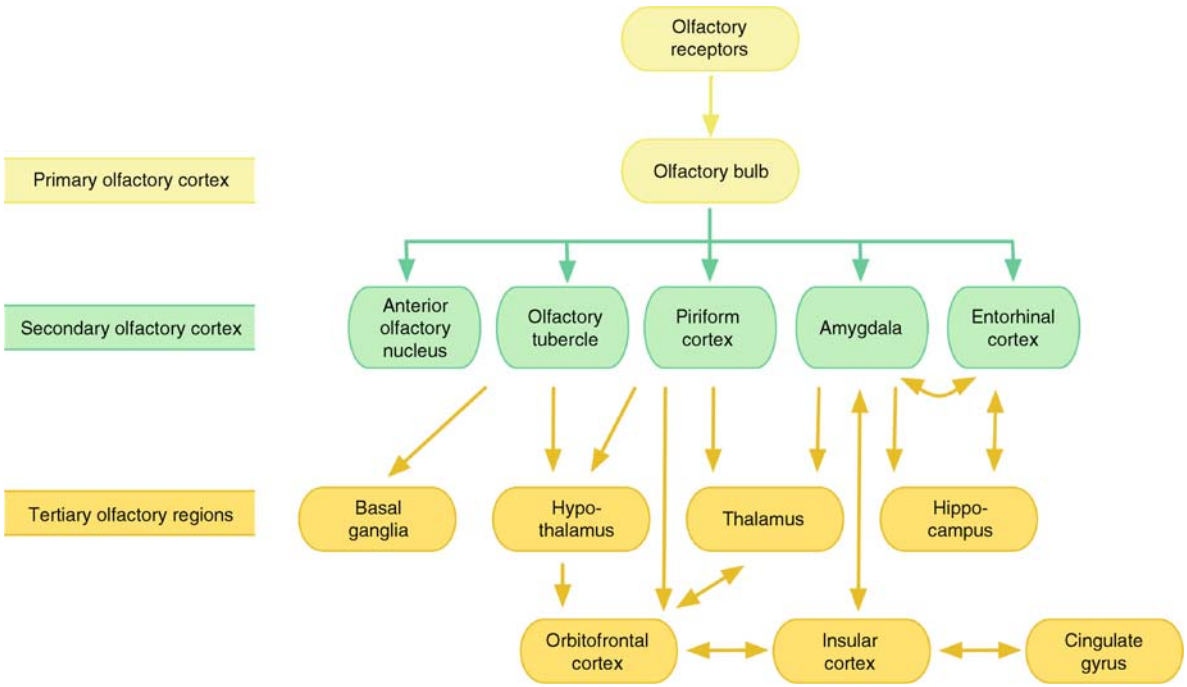
►Olfactory receptors (OR): Olfactory receptor neurons are located in the olfactory epithelium, on the roof of the nasal cavity, above or below the anterior middle turbinate insertion, and are covered by a layer of olfactory mucosa. In humans, several million olfactory receptor neurons are found in both nasal cavities constituting the first-order neurons of the olfactory system. Olfactory receptor neurons are the only sensory neurons in the human body that are directly exposed to the external environment and can therefore be damaged by external harmful substances. Thus the average lifetime of the neurons is only a few months. Afterwards they are replaced through differentiation of neuronal stem cells [4]. It is known that cAMP or cGMP gated ion-channels activated by G_{olf}-protein coupled receptor proteins are responsible for odor induced activity of olfactory receptor cells. Between 350 and 400 different types of olfactory receptors are found in the human nasal mucosa. Every olfactory receptor cell expresses only one or maybe two of odorant receptor types. In addition, all neurons expressing the same receptor protein send their axons to the same two glomeruli in each olfactory bulb. In vertebrates, an olfactory stimulus, e.g., the odor of roses, does not activate one specific OR only. Instead, a large number of receptors are activated, although the intensity of activation differs between all of them. A different olfactory stimulus will activate a different set of ORs, of which some may have been activated by the first stimulus as well, while others may not. Again, however, there is a characteristic intensity pattern of the activated receptors. Hence, quality coding seems to be related to neuronal analysis of the topographical distribution of activated receptor proteins [5].

►Olfactory nerves: The axons from the olfactory receptor neurons group into small bundles to form the olfactory nerves, or Fila olfactoria. On average, 12–16 branches of olfactory nerves run along the nasal septum on each side medially and additionally 12–20 branches course along the lateral wall of each nasal cavity [2].

►Olfactory bulb: The olfactory nerves run upwards through the foramina of the cribriform plate of the ethmoid, entering the anterior cranial fossa. On the way from epithelium to olfactory bulb the axons regroup to form more homogeneous bundles. The olfactory nerves terminate at the ipsilateral olfactory bulb. The two olfactory bulbs, one on each hemisphere, lie in a bony groove formed by the cribriform plate. In the olfactory bulb, the axons of the olfactory receptor neurons synapse with dendrites of second-order neurons in the olfactory system (mitral and tufted cells) forming discrete glomeruli.

Secondary Olfactory Cortex

The olfactory bulbs are connected to the secondary olfactory cortex via the ►olfactory peduncles. The olfactory peduncles consist of the olfactory tracts as well as a thin layer of grey matter which belongs to



Olfactory Pathways. Figure 1 Schematic illustration of the major central nervous projections of the olfactory receptor neurons. Shown are the three parts of the olfactory pathways (olfactory receptors/primary olfactory cortex, secondary olfactory cortex, and tertiary olfactory regions) and their connections.

the anterior olfactory nucleus. The postsynaptic axons of the mitral and tufted cells leave the olfactory bulb forming the lateral olfactory tract, one on each hemisphere. The lateral olfactory tract is situated in the ►olfactory sulcus of the orbital surface of the frontal lobe, lateral to the gyrus rectus. It transfers olfactory information to a number of ipsilateral brain areas within the posterior orbital surface of the frontal lobe and the dorsomedial surface of the temporal lobe [5]. Unlike in several non-mammalian species, there is no medial olfactory tract in mammals, including primates [4]. The lateral olfactory tract runs along the olfactory sulcus until it reaches the rostral part of the ►anterior perforated substance, where it divides into three roots, or striae. This area is called the ►olfactory trigone. The medial olfactory stria curves upwards to the ►septal region. The lateral olfactory stria curves laterally and leads to the medial surface of the temporal lobe. Delineated by the medial and lateral striae is the anterior perforated substance. The posterior border of the anterior perforated substance is delimited by a band of fibers that passes from the amygdala to the ►septum pellucidum. This band is called the diagonal band of Broca. The intermediate olfactory stria continues onto the anterior perforated substance, ending at the olfactory tubercle. Although well documented in animals, the intermediate and medial striae are extremely rudimentary in humans. Thus the lateral olfactory stria provides the only source of bulbar afferents to the brain. All areas receiving a direct projection from the lateral olfactory stria constitute the secondary olfactory cortex, consisting of the anterior olfactory nucleus, the olfactory tubercle, the piriform cortex, parts of the amygdala (periamygdaloid cortex, anterior and posterior cortical nuclei, nucleus of the lateral olfactory tract) and a small anteriomedial part of the entorhinal cortex.

►Connections within the secondary olfactory cortex: In rodents and carnivores, it has been shown that there is an extensive system of associational connections within the areas of the secondary olfactory cortex [4]. These fibers originate in all of the olfactory areas except the olfactory tubercle. Many of the associational fibers also extend into cortical regions beyond the areas that receive fibers from the olfactory bulb, including portions of the entorhinal, perirhinal, and insular cortex, and the medial amygdaloid nucleus.

►Contralateral connections: The projection of the olfactory bulb itself is entirely unilateral. However, fiber bundles from the olfactory peduncle cross in the ►anterior commissure to reach the contralateral olfactory bulb and cortex, providing the major route of interhemispheric olfactory information transfer. Although these fibers run with the olfactory tract, they do not originate from mitral or tufted cells of the olfactory bulbs. Instead, they originate from those cells of the anterior olfactory nucleus, which are located

in the olfactory bulb. Similar commissural fibers also originate more caudally, in the anterior part of the piriform cortex [4]. In humans all contralateral olfactory projections exert inhibitory effects only.

►Centrifugal projections to the olfactory bulb: Many of the olfactory cortical areas, including the anterior olfactory nucleus, piriform cortex, and periamygdaloid cortex send fibers back to the olfactory bulb. The projection of the anterior olfactory nucleus is bilateral. There is also a substantial projection from the nucleus of the horizontal limb of the diagonal band to the superficial layers of the olfactory bulb.

So far, a clear transformation of the highly ordered topographic map of the bulb onto the olfactory cortex has not been demonstrated. Small areas of the olfactory bulb project to virtually the entire olfactory cortex, and small areas of the cortex receive afferents from virtually the entire olfactory bulb [6]. However the results of a recent genetic tracer study in rodents indicate that a given olfactory receptor subtype projects to discrete neuronal clusters within the olfactory cortex, suggesting a topographical organization in olfactory cortex which is similar to the bulbar organization [7].

►Piriform cortex: The piriform cortex is the largest olfactory cortical area in humans as well as in most mammals. It is situated along the lateral olfactory tract on the caudolateral part of the orbital cortex, near the junction of the frontal and temporal lobes, and continues onto the dorsomedial aspect of the temporal lobe. Due to this it is defining two subdivisions: the anterior (frontal) piriform (or "prepiriform") cortex and the posterior (temporal) piriform cortex. Both parts of the piriform cortex are histologically identical. However it has been suggested that human frontal and temporal piriform cortex are functionally distinct [5]. The piriform cortex is activated by olfactory stimuli but habituates rapidly to repetitive stimulation. It has been shown "that sniffing, whether an odorant is present or absent, induces activation primarily in the piriform cortex" [8] leading to the assumption that the sniff primes the piriform cortex for an optimal perception of an odor [5]. It is suggested that the temporal part of the piriform cortex mediates basic odor perception independent of odor valence while the frontal part of the piriform cortex is receptive to hedonic value of the odor. Additionally the piriform cortex is involved in olfactory learning and memory [5].

►Amygdala: Projections from the olfactory bulb terminate in several discrete portions of the amygdala (periamygdaloid region, anterior and posterior cortical nuclei, nucleus of the lateral olfactory tract). The cytoarchitectonic transition from the amygdala to the temporal piriform cortex is poorly demarcated. The olfactory areas of the amygdala send projections back to the bulb as well as provide direct input to lateral, basolateral, central amygdaloid nuclei and to basal ganglia, thalamus, hypothalamus, and prefrontal cortex [5]. It is suggested that the amygdala is highly responsive to odor stimulation. The amygdala is proposed to play an important role in affective responses in general, and in olfactory hedonics in particular. The amygdala is responsible for the interaction between valence and intensity of an odorant, as well as for olfactory memory. Of all the senses, olfaction possesses the most intimate relation with the amygdala.

Tertiary Olfactory Regions

From secondary olfactory cortex, information is transmitted to several other parts of the brain, including orbitofrontal cortex, agranular insular cortex, additional subnuclei of the amygdala, medial and lateral hypothalamus, medial thalamus, basal ganglia, and hippocampus. These areas have been referred to as tertiary olfactory regions. Projections to and among these areas are complex and cannot be discussed here in detail. Most of these areas are not specific for processing of olfactory stimuli and show activation by other sensory inputs as well. This complex network of brain areas provides the basis for odor-guided regulation of behavior, feeding, emotion, autonomic states, and memory [5].

►Orbitofrontal cortex (OFC): The OFC is situated at the basal surface of the frontal lobes. It receives input from all secondary olfactory regions (except the olfactory tubercle) in the absence of an obligatory thalamic intermediary and in turn provides feedback connections to each of these regions. The OFC represents the main neocortical projection site of the olfactory cortex and is responsible for initial processing of olfactory information [5]. There is converging evidence that specialized areas within the OFC are engaged depending on the specific task of olfactory processing and that there is some functional lateralization. The posterior OFC is known to be associated with low-level aspects of olfactory processing, such as passive smelling and odor detection whereas the anterior OFC is engaged with higher-order olfactory processing, including associative learning, working memory, and odor recognition memory. Additionally there is evidence for different brain activation associated with odorants of different pleasantness. Whereas pleasant odors evoke activity in medial OFC, unpleasant odors lead to an activation in lateral OFC. Furthermore the OFC receives input from other sensory areas, especially from gustatory, visual, and visceral centers, providing the basis for multisensory integration, resulting in feeding-related and odor-guided behaviors [5]. A functional imaging study demonstrated that regions of the OFC are related to olfactory sensory-specific satiety [9]. The activation of some regions within the OFC produced by the odor of a food eaten to satiety decreased, whereas there was no similar decrease for the odor of food which was not eaten in the meal.

Other Brain Areas Involved in Olfactory Processing

►Cingulate: Although there are connections between the cingulate gyrus and frontal areas involved in olfaction, the cingulate gyrus has not typically been considered as a part of the olfactory system. The cingulate gyrus is involved in processing of information of various kinds. More specifically, the anterior cingulate is frequently involved in tasks requiring attention to sensory features in the environment. In olfactory studies, activations have been reported in anterior as well as in posterior parts of the cingulum. Interestingly, the cingulate gyrus has also been reported to be of critical importance in the processing of painful sensations. Thus, one might speculate that emotions induced by either odors or pain relate to a similar pattern of brain activation in the cingulate gyrus [2].

►Cerebellum: In several studies, cerebellar activation following olfactory stimulation has been reported. Yet, the functional significance of these findings remains unclear. In a functional imaging study the effects of smelling versus sniffing an odor on cerebellar activation were compared and it was hypothesized that the cerebellum maintains a feedback mechanism that regulates sniff volume in relation to odor concentration [10].

In conclusion, functional imaging data support a model of hierarchical organization of olfactory processing. From the ORs and olfactory bulbs (primary olfactory cortex), information are projected to the secondary olfactory cortex. The piriform cortex is the most prominent part of the secondary olfactory cortex in man. Neuroimaging as well as neuroanatomical data suggest that this area is at least minimally engaged during all olfactory tasks. A variety of tertiary regions have been shown to receive projections from the secondary olfactory cortex, among which the OFC seems to be engaged in most tasks of olfactory processing. Thus, core areas within the olfactory system may play a mandatory initial role. However, the involvement of tertiary regions seems to vary with specific task demands, e.g., whether odor processing is related to recognition or emotional response. Finally, another level of organization appears to involve brain areas that fall outside of the typically defined olfactory system, which become engaged during specific types of processing. Examples of these areas are the activation of the cingulate cortex as a multimodal sensory processing area or involvement of the cerebellum which is involved in the adjustment of sniff volume in regard to odor concentration. The ipsilateral nature of olfactory projections, the absence of the thalamic relay during information transmission to the cortex, and the overlap with limbic brain areas are properties of the olfactory system, which sharply distinguish olfaction from other sensory modalities. In summary, odor processing seems to comprise a serial processing of information from primary to secondary and tertiary regions, and also a parallel, distributed processing engaging a complex and distributed network of brain regions whose pattern of activation varies depending on the specific requirements of the task.

References

1. Weismann M, Yousry I, Heuberger E, Nolte A, Ilmberger J, Kobal G, Yousry TA, Kettenmann B, Naidich TP (2001) Functional magnetic resonance imaging of human olfaction. Neuroimaging Clin N Am 11(2):237–250
2. Wiesmann M, Kettenmann B, Kobal G (2004) Functional magnetic resonance imaging of human olfaction. In: Taylor AJ, Roberts DD (eds) Flavor perception. Blackwell, Oxford, pp 203–227
3. Cleland TA, Linster C (2003) Central olfactory structures. In: Doty RL (eds) Handbook of olfaction and gustation. Marcel Dekker, New York, pp 165–180
4. Price JL (2004) Olfactory system. In: Paxinos G, Mai JK (eds) The human nervous system. Elsevier, Amsterdam, pp 1197–1211
5. Gottfried JA (2006) Smell: central nervous processing. Adv Otol Rhinol Laryngol 63:44–69
6. Haberly LB, Price JL (1977) The axonal projection patterns of the mitral and tufted cells of the olfactory bulb in the rat. Brain Res 129(1):152–157
7. Zou Z, Horowitz LF, Montmayeur JP, Snapper S, Buck LB (2001) Genetic tracing reveals a stereotyped sensory map in the olfactory cortex. Nature 414(6860):173–179
8. Sobel N, Prabhakaran V, Desmond JE, Glover GH, Goode RL, Sullivan EV, Gabrieli JD (1998) Sniffing and smelling: separate subsystems in the human olfactory cortex. Nature 392(6673):282–286
9. O'Doherty J, Rolls ET, Francis S, Bowtell R, McGlone F, Kobal G, Renner B, Ahne G (2000) Sensory-specific satiety-related olfactory activation of the human orbitofrontal cortex. Neuroreport 11(4):893–897
10. Sobel N, Prabhakaran V, Hartley CA, Desmond JE, Zhao Z, Glover GH, Gabrieli JD, Sullivan EV (1998) Odorant-induced and sniff-induced activation in the cerebellum of the human. J Neurosci 18(21):8990–9001

Olfactory Peduncle

Definition

The olfactory peduncle runs bilaterally from the olfactory bulb to the anterior perforated substance. The olfactory peduncle contains the olfactory tract as well as thin layers of grey matter which are part of the anterior olfactory nucleus.

►Olfactory Bulb
►Olfactory Pathways
►Olfactory Tract

Olfactory Perception

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Synonyms

Olfactory awareness; Olfactory sensitivity; Olfactory discernment; Olfactory acuity

Definition

Olfactory ►perception is a process that starts in the nose with the stimulation of olfactory sensory neurons and terminates in higher cerebral centers which, when activated, make us consciously aware of an odor. In humans this awareness is generally confirmed by verbal reports while in animal studies some sort of odor detection or discrimination task is used. In mammals, olfactory stimuli are received and processed by multiple systems (the main olfactory system, vomeronasal, and the ►septal organ system). Activation (particularly by irritants) of trigeminal, ►vagal and glossopharyngeal receptors in the respiratory tract may contribute to the perceptual experience. However, most research has concentrated on the main olfactory system which also appears to be the only functional olfactory system in humans.

Among the more remarkable aspects of olfactory perception are a seemingly infinite number of odors and odor combinations that can be discriminated, that for humans, most odors generate an emotional response that can range from extreme disgust to extreme pleasantness, and that, in many species, odor exposure can exert profound influence on social, including reproductive, behavior. The neuroscience of olfactory perception has been driven largely by these and related behavioral outcomes and may be viewed as attempts to understand their neurobiological basis.

Characteristics

The Biological Basis of Odor Perception

Molecular biological studies identifying the large family of odorant receptor genes have revealed principles in the organization of sensory neurons and their pattern of projection to the olfactory bulb. Each sensory neuron expresses one of a large number of receptor proteins (about 1,000 in rodents) and the axons of neurons that express the same receptor converge to terminate in the same glomerular areas in the olfactory bulb. While receptor–ligand interactions define which odorant molecules will activate a sensory neuron, the stimulus spectrum (range of sensitivity) of any one sensory neuron appears broadly rather than narrowly tuned. Consequently, each class of neurons may respond to a wide variety of odorants, more strongly to some, more weakly to others (depending on structural interactions of ligand–receptor binding). As a result, many and perhaps hundreds, of different classes of sensory neurons may respond more or less strongly to even simple (monomolecular) odorants [1,2].

The inputs to the bulb from sensory neurons are relayed to more central brain areas by second order (mitral and tufted) cells whose axons converge to form the lateral olfactory tract, the primary projection pathway from the bulb to the brain. Although the olfactory cortex (piriform and lateral entorhinal cortices) is the primary termination for these outputs, there are fairly direct projections to four other target areas: prefrontal orbital cortex (via the dorsal medial thalamic nucleus), hippocampus (via the lateral entorhinal cortex), the corticomedial division of the amygdala, and the hypothalamus [3]. As described below, it is tempting to associate each of these projection targets with different known olfactory functions: analysis of complex olfactory signals (primary olfactory cortex), acquisition of cognitive based olfactory tasks and, perhaps, conscious awareness of an odor (the medial dorsal thalamic-orbital frontal cortex system), excellent olfactory memory (the entorhinal–hippocampal system), emotional component of odors (amygdala, limlaic system), and olfactory influenced neuroendocrine changes (projections to hypothalamus).

Odor Quality Perception

Perhaps the most active area of research relevant to olfactory perception concerns the neural mechanisms that code for odor discrimination and odor quality. Work here has concentrated largely on the olfactory bulb because the functional organization of its inputs is now well understood and because bulbar activity in response to odor stimulation can be visualized using a variety of methods including functional magnetic resonance imaging (fMRI), optical imaging of intrinsic signals, indexing increases in metabolic activity using 2-deoxyglucose (2-DG) and expression of molecular activity markers such as c-FOS [2].

The so-called "combinatorial" view of odor coding is the most widely accepted explanation for the physiological basis of odor quality perception. The convergence of inputs from sensory neurons expressing the same type of receptor plus the many different types of sensory neurons that respond to any one odor results in activation of multiple discrete regions in the olfactory bulb upon odor stimulation. Although structurally similar odors may activate similar or overlapping areas in the olfactory bulb, in all cases examined, each odor produced a unique pattern of glomerular activation.

This "odotopy" or odotopic map representation of different odors at the level of the olfactory bulb provides the primary evidence for the generally accepted "combinatorial" view of odor coding.

While the details of this scheme are topics in other chapters of this volume, its potential significance for understanding odor perception is clear: according to this view, the pattern of inputs from the sensory epithelium to the olfactory bulb provides the neural basis for odor discrimination and, hence, largely determines the perceived quality of an odor. In general, this combinatorial hypothesis has considerable face validity; it provides a reasonably parsimonious account of odor coding, and is solidly grounded in both the molecular biological studies on the organization of inputs to the olfactory bulb and the results of numerous mapping studies. Nevertheless, this view has been challenged by results obtained using fast imaging methods, by studies using awake, behaving animals, and by recent work suggesting that the organization of olfactory cortex may be more suitable for coding complex odor signals.

Temporal Parameters and Early Events in the Olfactory Bulb

The minimum time required to identify a stimulus helps define the temporal period during which neural coding occurs. Both human and animal subjects can identify an odor after only a few hundred milliseconds of exposure (i.e., after one or two sniffs). What neural events occur during this brief period? Fast imaging methods demonstrate that, within the first few hundred milliseconds of odor exposure, activity across the glomerular layer of the olfactory bulb evolves, is temporally complex and that responses to different odors vary in many parameters including latency of onset, rise time, amplitude, modulation by respiration cycle, temporal dynamics of activation, sniff rate, and the extent to which rise time and amplitude are correlated [4]. The important point is that within the brief time needed to identify an odor, numerous neural events are potential candidates for odor coding. Because odotopic maps of the olfactory bulb are based on averaging activity over many seconds or minutes of odor exposure, it remains unclear whether such maps represent the temporally dynamic changes that occur during the first few sniffs of an odor [2].

Disruption of Bulbar Inputs

One method for examining the functional significance of odor maps is to assess odor detection and discrimination after surgical or toxicant destruction of bulbar sites activated by a target odor. Surprisingly, even extensive disruption in the patterns of bulbar inputs in rats fails to produce a specific anosmia or hyposmia, or to significantly disrupt ability to discriminate between odors [5]. In related behavioral studies only mixed results have been obtained in attempts to assess other predictions based on the proposed odotopic view of odor coding (e.g., that similarity in patterns of bulbar activation should predict perceived similarity or difficulty in discriminating between odors).

Perception of Complex Odors and the Olfactory Cortex

The question of whether we experience the individual components of odorant mixtures (i.e., analytic perception) or as a single odor (i.e., synthetically) is complex because, in mixtures, odorants having different vapor pressures and solubilities may produce complex outcomes, and the resulting molecules probably compete for sites on olfactory sensory neurons. Nevertheless, except in the laboratory, most odors encountered represent complex mixtures of vapors. Behaviorally, the issue has been largely resolved by a variety of studies in which human subjects are asked to identify the number of or components of different odors in mixtures. Even with training, subjects are rarely able to identify individual components or accurately identify the number of components in mixtures of three or more odorants.

The evidence from these and related studies strongly supports the view that olfaction is synthetic and that complex mixtures, such as the many volatile molecules that contribute to the odor of urine or coffee, are perceived as single odor "objects." It follows then that analytic or feature detection functions that occur at the level of the olfactory bulb may be early events in further signal processing that result in mixtures being perceived as a single identifiable odor. Where might such synthesis occur? The organization of inputs from olfactory epithelium to the olfactory bulb effects a relatively simple transformation in which signals from sensory neurons expressing the same membrane receptor are represented in spatially discrete areas of the bulb. In contrast, bulbar output neurons are subject to numerous synaptic interactions within the bulb as well as feedback from ►centrifugal projections originating in deeper brain structures and have extensive connections within olfactory cortex. These provide the opportunity for more complex modification in the representation in olfactory cortex of the initial sensory signals. For example, whereas mitral/tufted cells in the olfactory bulb receive input from just a single type of odor receptor, each neuron in the olfactory cortex appears to receive information from multiple bulbar output neurons and some neurons are activated only if two different odor receptor signals are received. Further, responses in olfactory cortex may have considerable plasticity: unit responses to components of odor mixtures are readily modified by exposure to the mixture and, in trained animals, modified as a function of whether the odor was associated with a reward [6].

In brief, our understanding of the biological basis of odor quality perception is incomplete. The results of behavioral studies with rodents, the enumeration of neural events during odor sampling and initial studies on olfactory cortex provide important data but not, as yet, an alternative scheme of odor coding.

Perceptual Subqualities

Can odors be classified into types or subqualities? For other modalities stimulation produces only a limited number of qualitative differences or subqualities such as the basic types of tastes, skin sensation, colors or tonal frequencies that can be discriminated. For olfaction, literally thousands of monomolecular odorants may each produce a qualitatively different perception, and combinations of odorants may produce additional unique qualitative experiences. A number of odor classificatory schemes have been proposed, some of which are based on multivariate analyses of odor judgments by a panel of subjects sampling a wide variety of odors. None, however, are able to accommodate the full range of perceptual experience generated by monomolecular odors or have strong predictive value for how a novel odorant or a mixture of odorants would be judged. Nevertheless, there appears to be reasonably broad agreement for a limited number of descriptors (such as camphor, musk, floral, peppermint, ether, pungent and putrid, the seven primary odors suggested by Amoore) and such schemes have heuristic value. However, odorants within any such class often have diverse physiochemical properties and, with few exceptions, it has not proven possible to reliably predict odor quality from the molecular structure of an odorant.

Affective Responses to Odors

Few olfactory stimuli are judged as hedonically neutral; most elicit a clear like or dislike reaction on the part of the perceiver. The ubiquitous use of odorants in cosmetics and foods attests to the fact that many odors are pleasing and can influence mood and appetite. In humans, the hedonic valence of an odor is largely learned and the experience associated with an odor probably determines its hedonic valence. There are obvious cultural differences in odor preference: for example the odor of the durian fruit is judged generally as fetid by Westerners but is described as heavenly by natives in South East Asia.

►Trigeminal, ►glossopharyngeal and vagus nerves in the respiratory tract respond to airborne irritants and their activation together with olfactory sensory neurons may contribute to perceived intensity and unpleasantness of some odors. Except for fear or aversive responses shown by some animals to the odor of predators, it has proven difficult to assess odor preferences in laboratory animals. Human fMRI studies demonstrate arousal of the amygdala by both pleasant and unpleasant odors but, interestingly, not by more neutral odors. These outcomes are in agreement with the more general findings that the amygdala plays an important role in emotional arousal.

Odor Memory

The "Proust effect" provides a popular example of long-term odor memory, and déjà vu phenomena are often triggered by odors. Clearly, odors, particularly those associated with an emotion arousing event, are remembered for years if not the lifetime of an individual. Studies with rodents demonstrate near perfect retention of odor discrimination tasks even after a brief exposure to the conditioning odor or after manipulations specifically designed to maximize proactive and retroactive interference with odor memory [7]. Where such long-term memories are stored is uncertain; in rats, neither surgical disruption of the olfactory thalamic-orbital prefrontal cortex or projections to the amygdala disrupt odor memory. In humans, fMRI studies reveal activation of many brain areas during the encoding of odor stimuli but more restricted areas and especially olfactory cortex and orbital prefrontal areas in recall or identification of familiar odors.

Cognitive Function

In humans, olfaction is generally not viewed as an essential sensory modality and does not appear to play an important role in cognitive or higher mental processes (i.e., we don't "think with our noses"). In contrast, rats, whose behavior is largely guided by and dependent on odors, become quite competent in performing complex, cognitive based tasks when odors are provided as discriminative cues. Thus, rats quickly acquire strategies for nearly errorless solutions for a series of simple discrimination tasks and more difficult matching to sample problems (i.e., they acquire a "learning set"), demonstrate paired associate learning, and even solve problems requiring a form of transitive inference. It is unlikely that other sensory cues could support such learning and, indeed, rats perform more poorly or fail when trained on learning set or matching to sample tasks if visual or auditory cues are used. These cognitive abilities appear to be dependent on thalamic-orbital frontal cortical projections: lesions of this system, including those confined largely to the olfactory component of the medial dorsal thalamic nucleus, have little or no effect on simple odor discrimination problems but disrupt acquisition of complex olfactory tasks [7].

Odors, Reproduction and Unconscious Perception

Olfaction is a critically important sensory modality for most mammals and is used in a variety of behaviors from homing to identifying sources of food and the social status of conspecifics. The demonstration that exposure of gravid female mice to the odor of males from a different strain can disrupt pregnancy (the

"Bruce Effect") led to studies demonstrating clearly the influence of conspecific odors on neuroendocrine changes involved in sexual maturity, mate selection and other aspects of reproduction and social interactions in rodents and, to some extent, in primates. Whether odors play a similar role in humans remains a continuing topic of interest. In humans, exposure to steroidal and other odors from exocrine glands appears to have subtle and gender-specific effects on a number of physiological indices and may alter mood [8,9]. Of particular interest is the evidence that such changes may occur without the subject's conscious awareness of the odor stimulus. It is unclear whether this "unconscious perception" is mediated by neural pathways that bypass olfactory cortex. Such pathways exist in mammals with well developed vomeronasal/accessory olfactory bulb structures but there is scant evidence for the existence of a similar accessory olfactory system in humans.

Olfaction, Schizophrenia and Neurodegenerative Disease

Deficits in odor identification together with signs of degeneration in central olfactory structures are a pervasive concomitant of schizophrenia, Wilson's, Parkinson's disease (PD) and Alzheimer-type dementia (AD). Patients diagnosed as schizophrenic perform poorly on an odor identification task despite having reasonably normal odor detection thresholds. Indeed, olfactory dysfunction may be near universal in neurodegenerative diseases and occurs even in those with cerebellar ataxia; its onset may predate the first clinical signs of the disease and, thus, be diagnostic, particularly for patients at risk for psychosis or AD (e.g., those with an ApoE4 allele).

Other sensory systems do not exhibit the extensive degenerative changes that occur in the olfactory system in PD and AD and it is unclear why a progressive loss of smell function should be characteristic of and even predate movement and cognitive disorders [10].

In brain imaging studies, identification deficits appear to be more closely associated with changes in olfactory cortex or the temporal lobe than with the frontal lobe. Interestingly, olfactory auras often precede the onset of temporal lobe psychomotor epilepsy. The temporal lobe may also be involved in other olfactory disorders including olfactory hallucinations (phantosmia) and altered or distorted perception of odors (parosmia).

References

1. Buck LB (1996) Information coding in the vertebrate olfactory system. Annu Rev Neurosci 19:517–544
2. Wachowiak M, Shipley MT (2006) Coding and synaptic processing of sensory information in the glomerular layer of the olfactory bulb. Semin Cell Dev Biol 17:411–423
3. Carmichael ST, Clugnet MC, Price JL (1994) Central olfactory connections in the macaque monkey. J Comp Neurol 346:403–434
4. Spors H, Wachowiak M, Cohen LB, Friedrich RW (2006) Temporal dynamics and latency patterns of receptor neuron input to the olfactory bulb. J Neurosci 26:1247–1259
5. Slotnick B, Bodyak N (2002) Odor discrimination and odor quality perception in rats with disruption of connections between the olfactory epithelium and olfactory bulbs. J Neurosci 22:4205–4216
6. Wilson DA, Kadohisa M, Fletcher ML (2006) Cortical contributions to olfaction: plasticity and perception. Semin Cell Dev Biol 17:462–470
7. Slotnick B (2001) Animal cognition and the rat olfactory system. Trends Cogn Sci 5:216–222
8. Snowdon CT, Ziegler TE, Schultz-Darken NJ, Ferris CF (2006) Social odours, sexual arousal and pairbonding in primates. Philos Trans R Soc Lond B Biol Sci 361:2079–2089
9. Jacob S, Hayreh DJ, McClintock MK (2001) Context-dependent effects of steroid chemosignals on human physiology and mood. Physiol Behav 74:15–27
10. Albers MW, Tabert MH, Devanand DP (2006) Olfactory dysfunction as a predictor of neurodegenerative disease. Curr Neurol Neurosci Rep 6:379–386

Olfactory Perceptual Learning

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Synonyms

Odor memory; Odor familiarity; Odor expertise

Definition

Perceptual learning is an improvement through experience in the ability or potential ability to detect and/or discriminate sensory stimuli. Perceptual learning can be demonstrated in nearly all sensory systems, for example through the enhanced ability of musicians to identify or discriminate musical notes, or of visual artists to identify similar colors. In the sense of smell, most ►odors experienced in nature or everyday life are complex mixtures of many different ►odorant molecules. Being able to discriminate these different mixtures from each other is one of the main functions of the olfactory system. In mammals, recognition and discrimination of such odors appears to involve an initial analysis of the inhaled stimulus into its component molecular and submolecular features, and a subsequent merging of those features into a unitary odor object, such as "coffee" or "rose." As odors become more familiar, both the encoding of the features and their synthesis into objects are enhanced, leading to improvements in fine

sensory discrimination. Experience-dependent changes within the nervous system underlying this olfactory perceptual learning occur throughout the olfactory sensory pathway.

Characteristics

Sensory discrimination - the ability to determine whether two stimuli are the same or not - can improve with experience. Slight differences between two stimuli that originally went undetectable, can become detectable with experience and training. This experience-dependent improvement is called perceptual learning, and generally regarded as a form of ►implicit learning, not requiring conscious awareness. Typical examples of perceptual learning include improvements in visual vernier acuity, where the ability to determine whether two vertical lines are either exactly in line or slightly horizontally displaced from each other can be improved through training. Similar examples have been described for auditory pitch perception and haptic (sense of touch) texture discrimination. One common characteristic of perceptual learning is that the effect is largely limited to the familiar stimulus set. Thus, improvements in vernier acuity for vertical lines does not transfer to acuity for horizontal lines.

The improvement in sensory discrimination with experience implies a change in the underlying sensory system which encodes the stimuli. Sensory systems generally encode stimuli in the external world by having populations of neurons tuned to slightly different aspects of those stimuli. Thus, peripheral receptors, transducing sensory input into neural activity, may only respond to a narrow range of energy – a certain wavelength or location of light in vision, a certain frequency of sound in audition, or a certain molecular shape or charge in olfaction. Through the cooperative action of large ensembles of such neurons, information about the identity of the original stimulus emerges, which can then guide perception and behavioral responses.

This basic sensory system function leads to several potential mechanisms through which perceptual learning may arise. Experience with a specific range of sensory inputs could lead to changes in peripheral receptor number or relative tuning distribution, tuning of neurons within the central nervous system, and/or local circuit interactions within the large ensembles. There is evidence for all of these experience-dependent changes occurring in the olfactory system associated with perceptual learning.

Behavioral Evidence of Olfactory Perceptual Learning

In humans, experience with specific odors enhances subsequent discrimination and identification of those odors. Thus, familiar odorants are more easily discriminated than unfamiliar odorants [1]. This experience-dependent improvement can be induced either through specific exposure or training, or emerge over a lifetime of experience. This latter process may contribute to strong cultural differences in perception and categorization of odors.

In animal models, as in humans, odor experience enhances discriminability of familiar odors [2,3]. Naïve rodents, for example, fail to respond differentially to many monomolecular odorants differing by a single hydrocarbon in their molecular structure. This can be tested in a habituation/cross-habituation paradigm, where one odorant is repeatedly presented until some behavioral response habituates. Then, a second odorant is presented. If the animal discriminates between the odorants, the new odorant evokes a behavioral response. If the animal does not discriminate between the odorants, the response to the new odorant is comparable to the habituated odorant. Using such a paradigm, naïve animals that were habituated to, for example the four carbon odorant molecule ethyl butyrate, showed cross-habituation to the five carbon odorant molecule ethyl valerate, suggesting they cannot discriminate between these odorants (i.e., the odors are similar). However, if given prior experience with these odorants, they subsequently do show differential responses to the two odorants. These experience-induced changes appear selective to the familiar odorants and do not create a general enhancement for discrimination of all odorants.

In addition to experience-induced enhancement of odorant discrimination, perceptual learning can also improve identification of components within odorant mixtures [4]. With simple mixtures of pure odorants, the intensity of individual components plays a major role in the ability to identify those components. Thus, as might be expected, as one component within a binary mixture becomes more intense (higher relative concentration) than the other, that component comes to dominate the perception of the mixture. However, familiarity of the components produces a similar effect. Familiar components are more easily identified within a mixture than unfamiliar components. This consequence of perceptual learning may underlie the ability of professional flavorists and perfumers to identify components with mixtures, although human psychophysical data suggest even professionals have only a limited ability to analyze complex mixtures that include greater than 3–4 components into their constituent parts.

Finally, in addition to experience-induced enhancement of discriminability, odorant exposure may also enhance detectability of odorants [5]. Perhaps the best example of this is perception of the odorant androstenone, though other odorants show similar effects. Androstenone is a component of human sweat, and is more concentrated in males than females. Many individuals appear to have very high thresholds for detecting androstenone, or are even ►anosmic to it. However, repeated exposure over multiple days can significantly improve detection in these individuals, dramatically lowering detection thresholds. There is some evidence

that females may acquire this experience-dependent sensitivity faster than males.

Neurobiology of Olfactory Perceptual Learning

At the neurobiological level, memory for odors and their associations is distributed throughout the sensory pathway, with evidence for changes from the receptor sheet all the way to the primary olfactory cortex [2,6]. The olfactory systems of all vertebrates and many invertebrates share several basic structural features. Peripheral olfactory receptor neurons express one or a few olfactory receptor genes which code for proteins that bind to odorant molecules sharing a particular structure. These receptor neurons then project to the second order neurons within a central nervous system structure called the olfactory bulb (vertebrates) or antennal lobe (invertebrates). The connections between receptor and second order neurons occurs within structures called glomeruli, which receive input from receptor neurons all expressing the same olfactory receptor genes. Thus, stimulation with a particular odorant activates a unique combination of glomeruli based on which receptors that odorant molecule binds. The response of second order neurons reflects the homogeneous receptor input, as well as local circuit interactions. The second order neurons then project to the olfactory cortex (mammals) or mushroom bodies (invertebrates), where convergence of the different molecular features extracted by the periphery occurs on individual third order neurons. In different behavioral paradigms and different species, olfactory experience has been found to change the response patterns of receptor neurons and glomeruli, and both single cell and ensemble activity of second and third order neurons.

Experience-induced responsiveness to odorants, such as androstenone, may involve both peripheral and central changes. Evidence in humans and rodents suggests that repeated or prolonged exposure to an odorant such as androstenone produces enhanced olfactory receptor sheet responses as measured with electro-olfactogram [7]. The electro-olfactogram is a measurement of summed receptor sheet activity, much as the electroencephalogram measures summed cortical activity. The specific mechanism of enhanced receptor sheet responsiveness to exposed odors in currently unknown. In addition to these peripheral changes, there is some evidence for central sensitization [5]. Humans exposed unilaterally to androstenone will become able to smell it through either nostril, despite the lack of a direct connection between the two receptor sheets. This suggest that central neurons, that receive convergent information from the two airways, may partially mediate the exposure-induced sensitization.

Experience-induced enhancements in discrimination appear to rely on changes within the central nervous system. Exposure to an odor for as little a few minutes can produce a long-lasting shift in the tuning of second order neurons, such as olfactory bulb mitral cells [3]. These shifts enhance the number of second order neurons encoding familiar odorant features. These changes in individual neuron activity are accompanied by large scale neural ensemble changes, as evidenced by changes in odorant-evoked local field potentials within the olfactory bulb. At least two mechanisms may contribute to these changes in stimulus-evoked activity. First, connectivity between existing neurons may be altered during perceptual learning through synaptic plasticity. Plasticity of synapses within glomerular and/or between second order neurons and local interneurons could affect feedback, feedforward and lateral inhibition. These changes in inhibition could influence both responses of single neurons to familiar stimuli and timing of evoked activity. A change in odorant-evoked spike timing, for example increased synchrony, is hypothesized to enhance the salience of familiar stimulus features to downstream neurons, thus facilitating their identification and discrimination.

A second mechanism of perceptual learning associated change within the olfactory bulb is anatomical restructuring of local circuits. A major class of local interneurons in the mammalian olfactory bulb, granule cells, undergo continual neurogenesis throughout life in many animals. Survival and incorporation of granule cells into local circuits is dependent on odor experience. Given the precise projections of olfactory receptor neurons to olfactory bulb glomeruli, different stimuli evoke different spatial patterns of activity across the olfactory bulb, with activation of a given glomerulus associated with activity of a local, spatially defined column of second order neurons and interneurons such as granule cells. Repeated stimulation of a given glomerulus over several weeks by exposure to a particular odorant, enhances survival of granule cells near that glomerular column, while sensory deprivation reduces granule cell survival [8]. Granule cells not only control excitability of second order neurons, but are also the target of cortical feedback to the olfactory bulb. Thus, they may play an important role in familiarity induced effects on olfactory bulb odor encoding.

Finally, olfactory perceptual learning is associated with changes within mushroom bodies of invertebrates and olfactory cortex of mammals [2,9]. As noted above, the olfactory cortex is hypothesized to synthesize disparate, co-occurring odorant features into perceptual wholes, or odor objects. As this synthesis occurs, a template is formed in cortical circuits, allowing a rapid match of subsequent input to that stored template and enhanced discrimination and recognition. This cortical learning may also contribute to perceptual stability of complex odors, even in the face of slight alterations in intensity or presence of some components [6]. Olfactory perceptual learning may involve changes in both the anterior and posterior piriform cortices, as well as the orbitofrontal cortex. In both humans [9] and rodents

[10], the anterior piriform cortex appears to encode stimulus identity, with experience creating a unique encoding of a mixture stimulus distinct from that of its components. In contrast, the posterior piriform cortex appears to encode information about odor quality (e.g., fruitiness) or categorical information, a process again enhanced by experience and odor familiarity.

The types of modifications in neural coding and perception described here associated with olfactory perceptual learning most likely occur in all cases when odors become familiar or are actively learned. The result is that our perception of familiar odors is different than our perception of novel odors, allowing enhanced discrimination and identification of the familiar.

References

1. Rabin MD (1988) Experience facilitates olfactory quality discrimination. Percept Psychophys 44:532–540
2. Davis RL (2004) Olfactory learning. Neuron 44:31–48
3. Fletcher ML, Wilson DA (2002) Experience modifies olfactory acuity: acetylcholine-dependent learning decreases behavioral generalization between similar odorants. J Neurosci 22:RC201
4. Livermore A, Laing DG (1996) Influence of training and experience on the perception of multicomponent odor mixtures. J Exp Psychol Hum Percept Perform 22:267–277
5. Mainland JD, Bremner EA, Young N, Johnson BN, Khan RM, Bensafi M, Sobel N (2002) Olfactory plasticity: one nostril knows what the other learns. Nature 419:802
6. Wilson DA, Stevenson RJ (2006) Learning to smell: olfactory perception from neurobiology to behavior, Johns Hopkins University Press, Baltimore, p 309
7. Wang L, Chen L, Jacob TJ (2003) Evidence for peripheral plasticity in human odour response. J Physiol 554:236–244
8. Lledo PM, Gheusi G (2003) Olfactory processing in a changing brain. Neuroreport 14:1655–1663
9. Li W, Luxenberg E, Parrish T, Gottfried JA (2006) Learning to smell the roses: experience-dependent neural plasticity in human piriform and orbitofrontal cortices. Neuron 52:1097–1108
10. Kadohisa M, Wilson DA (2006) Separate encoding of identity and similarity of complex familiar odors in piriform cortex, Proc Natl Acad Sci USA 103:15206–15211

Olfactory Plasticity

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Synonyms

Olfactory learning; Odor-exposure learning; Olfactory priming

Definition

Olfactory plasticity is a general term referring to all types of changes in odor-evoked responses resulting from individual experience. These changes, usually monitored behaviorally, rely on short- or longer-lived structural and/or functional modifications at different levels of the olfactory circuits. Olfactory plasticity is therefore a form of ►neural plasticity.

Characteristics

A general rule of sensory systems is that they constantly adapt to environmental conditions, inducing modifications of the way they process sensory stimuli. Such modifications can be very short (in the range of seconds, for instance receptor desensitization) or very long (in the range of years, plasticity of central representations), depending on the type of experience and of the species considered. Due to obvious differences in lifespan, modifications that are considered to correspond to a medium-term range in a given species may be assigned to the long-term range in a different species.

Olfactory plasticity is found in a wide range of species, from nematodes (*C. elegans*) to humans, with prominent examples in insects (fruit flies, bees, etc.) and mammals (rabbits, rats, mice, humans, etc.). These changes can affect all levels of the olfactory circuits, from the most peripheral (olfactory receptors) to the most central ones (cortical representation). Olfactory plasticity can be demonstrated in behavioral experiments, and its neural basis is usually the subject of neurophysiological and/or neuroanatomical experiments. We will first provide a brief description of a generalized olfactory system (for details, see essays on ►olfactory perception, or ►odor coding). We will then detail the types of sensory/associative experiences that induce olfactory plasticity at the behavioral level. To finish, we will present the current view of the neural basis of olfactory plasticity.

The Olfactory System

The anatomical organization of the olfactory system of vertebrates and of invertebrates, like insects, shows many fundamental similarities. Odors are detected at the periphery (olfactory mucosa within the nose *or* antenna) by olfactory sensory neurons (OSN), which each express a given type of olfactory ►G-protein-coupled receptor. These neurons relay odor information to a first olfactory centre, the olfactory bulb (OB) in vertebrates or its equivalent in insects, the antennal lobe (AL). Both structures are organized in a similar modular way: each of their subunits, the glomeruli, receives input from OSNs expressing the same olfactory receptor type. Glomeruli are sites of intensive synaptic contacts between several neuron types, in particular inhibitory neurons providing local inter-glomerular computation (periglomerular cells/local interneurons), and second-order neurons (mitral cells/projection neurons) that relay processed

information to higher brain centers. Between mitral cells, granule cells provide additional lateral inhibition in vertebrates. The complex ►neural network of the AL/OB is considered to be a major site for olfactory plasticity. It performs computations which are thought to mediate better discrimination between similar olfactory inputs, allowing more segregated spatio-temporal odor representations to be conveyed to higher brain centers such as the piriform cortex, the entorhinal cortex and the peri-amygdaloid cortex in mammals, or the mushroom bodies and the lateral protocerebral lobe in insects (see essay on ►odor coding). These structures are thought to be involved in higher-order processing of odor information, like providing the synthetic part of mixture representation, but also in associative learning and memory of odors, and, at least in mammals, providing emotional and hedonic values to odors. As we will see, olfactory plasticity can take place at all levels of the olfactory system.

Sensory and Associative Experience Inducing Olfactory Plasticity

Experimentally, olfactory plasticity is often demonstrated by the result of behavioral experiments, during which a particular olfactory experience induces changes in the way animals or subjects respond to odors. We will review these types of experiences from simple olfactory exposures to much more complex forms of associative learning between particular odors and different outcomes.

Olfactory Exposure

Simple odor exposure, even a very short one, can have consequences on the way the olfactory system will respond to subsequent odor presentations. The most peripheral of these phenomena is called ►olfactory adaptation [1], during which exposure to an odor (from very short pulses to stimulations of a few seconds) decreases reversibly the sensitivity of olfactory receptor neurons (usually in the range of seconds to a few minutes). Functionally, this is believed to allow an animal to constantly adapt its olfactory system to environmental odors, avoiding saturation of the cellular transduction machinery and thereby keeping the ability for the animal to detect more relevant short-lasting odors. Different forms of odor adaptation have been described, depending on the length of the odor stimulation inducing it (short or long puff) and the length of the adaptation (short or long-lived). These different forms are thought to depend on slightly different but interconnected cellular feedback loops within olfactory sensory neurons. Odor adaptation is considered to be reversible. Experimentally, it has provided previous researchers an interesting way of testing whether two odorants are detected by different or overlapping sets of olfactory receptor neurons, in so-called cross-adaptation experiments: animals are first exposed to a mono-molecular odorant A until they adapt to it. Then a second odorant B is presented. If response to B is affected by the former presentation of A, it suggests that detection of B depends on receptors used for the detection of A.

Simple odor exposures do not only affect the periphery, and the changes that they induce at the central level are then considered forms of ►perceptual learning . On a quantitative level, repeated presentations of an odor can have two kinds of effects. On the one hand, the probability of a behavioral response provided by an animal to the presentation of the odor (for instance, a startle or a sniffing response) will tend to decrease through repeated presentations of this odor. This effect is termed ►odor habituation . In some cases, even if a decrease of an odor-evoked response is observed, this effect can be more related to a reduction of the animal's attention or of its overall responsiveness than to a decrease of odor detection ability or changes in odor processing. In fact, repeated experience with an odor can have the opposite effect, reducing the olfactory detection threshold (odors are detected at lower concentration) and can even allow odor detection by seemingly anosmic subjects. On a more qualitative level, repeated experience with a range of different odors can greatly improve the discrimination ability of subjects among these, but also novel, odorants. Furthermore, experience with an olfactory mixture can strongly modify the way the individual components of the mixture are perceived. For instance, a given odor presented to a subject together with a "smoky" odor will tend to be perceived afterwards as smoky, while the same odor would smell cherry-like after being presented together with a "cherry" odor. Such effects are usually interpreted as forms of ►implicit memory and are thought to rely on neural plasticity at different levels of central areas, from the OB where it would modify the receptive range of mitral/tufted cells to the piriform cortex and the orbito-frontal cortex where the synthetic representation of odors may change. These olfactory forms of perceptual learning can take place rapidly, but are usually long-lasting.

Associative Learning

The most prominent forms of olfactory plasticity relate to associative conditioning, during which animals learn to associate odors with particular outcomes or behaviors, which have a positive or negative significance for the animal. It is generally accepted that most of our hedonic relationship to odors is not innate, but rather acquired throughout our lifetime by associations between these

odors and particular events or contexts. Odor learning starts even before birth from the mother's amniotic fluid, as the olfactory system is already functional in utero by 12 weeks of gestation. For instance, children of mothers who consume particular odors (garlic, cumin, etc.) and were therefore exposed to these odors during gestation and/or breast-feeding show specific preferences for these odors afterwards. Throughout young age, children learn to associate particular scents or tastes with edibility and/or positive and negative events, and it is generally accepted that by the age of 8, most of our adult olfactory preferences are acquired, although adult experience certainly continues to shape olfactory preference [2]; see also learning during a sensitive period, below].

Experimental psychology distinguishes two main forms of associative learning which both are very prominent in the olfactory domain:

1. In ►classical (Pavlovian) ►conditioning , an animal learns to associate an originally neutral, ►conditioned stimulus (CS – here an odor) with a biologically relevant, ►unconditioned stimulus (US). For instance, honeybees learn to associate odors with sucrose solution in the paradigm of the proboscis extension response (PER) conditioning. In a hungry bee, sucrose solution triggers the reflex extension of the mouthparts (the PER), allowing the insect to drink. Prior to conditioning, odors are ineffective. However, after a single CS/US association, the odor can now elicit the PER and after a few such associations an odor-sucrose memory is formed that can last for the bee's lifespan.
2. In ►operant (instrumental) ►conditioning , the animal learns to associate a behavioral action to a ►reinforcement , and a ►discriminative stimulus (e.g., an odor) can function as a signal for producing the learned behavior. For instance, an odor may act as the signal for a rat to poke its nose in a particular box in order to receive a food reward. Although conditioning creates an association between nose poking and the food reward, odor-food and odor-poking associations are also built and will drive the rat's choice.

In both learning paradigms, odor-outcome (US or reinforcement) associations are established, which can be either ►appetitive or ►aversive.

More complex olfactory learning tasks can be conceived, either in a classical or an operant framework, establishing multiple associations between different odors and multiple outcomes. A simple example of such tasks is differential conditioning (A+, B−), in which an odor A is associated with a US/►reinforcer and another odor B is left without consequence. Experimentally, such conditioning has often been used in the study of neural olfactory plasticity [3–4], because it provides the experimenter with a within-animal control as the same animal has to learn to respond to odor A but not to odor B: usually, specific changes in neural responses are found for A but not for B. In some cases, learning can induce a decorrelation of the neural representations of A and B, making them more discernible for the olfactory system. More complex forms involve ambiguities between odors and outcomes, and give a special meaning to the concomitant presentation of two or more odors: for instance, in biconditional discrimination (AB+, CD+, AC−, BD−), each odor is as often reinforced as not, and the right behavioral response can only be found after linking different odor representations (here the animal should respond to odor A when it is presented together with B but not when A is presented together with C). All these different forms of olfactory learning are based on increasingly complex associations, and pose each different constraints to the olfactory system. In this case, one expects a decorrelation of the representations of odor combinations with different outcome, irrespective of the common presence of a given odor (e.g., AB+ vs. BD−).

Olfactory Plasticity During a Sensitive Period

The olfactory plasticity phenomena detailed above can take place at any moment in an animal's life. There are, however, instances of olfactory plasticity that can only happen during sensitive periods such as after mating or short after birth. Thus, newly-mated female mice learn the specific odor of the mating male, and any encounter with a different male will provoke pregnancy failure [5]. Another prominent example is neonatal learning in rabbit pups, which learn extremely fast – during the first three days after birth, odors that are present on the doe's belly. Recently, a mammary pheromone was found, which alone triggers stereotyped orocephalic movements of nipple search in young rabbit pups. Normally, odors do not elicit this response. However, a single simultaneous presentation of an odor together with the pheromone dramatically changes the pups' behavior, such that it will now respond to the odor presented alone [6]. This form of classical olfactory conditioning is particular, not only for the existence of a strict sensitive period, but also for the fact that an odor, the mammary pheromone, acts as a reinforcer.

Neural Basis of Olfactory Plasticity

Changes in odor-evoked behavioral responses can rely on neural plasticity at all levels of the olfactory circuits, from the most peripheral during olfactory adaptation to the more central, OB/AL and/or higher brain centers for perceptual and associative conditioning. Olfactory plasticity is manifested at the neuron level through both structural and functional neuronal changes.

On a structural level, the number and/or repartition of synaptic contacts between olfactory neuronal populations can be modified. For instance, differential olfactory conditioning is accompanied in ►pyramidal neurons of the piriform cortex by an increased density of ►dendritic spines linked to intra-cortex connections, but also to pruning (reduction) of spines linked to afferent input from the olfactory bulb, suggesting intense rearrangements of olfactory connectivity through learning [7]. Such structural changes can sometimes be correlated with a change in the volume or shape of neuronal structures like the glomeruli. In the particular case of the olfactory bulb, neural olfactory plasticity can take the form of the genesis and preferential survival of novel neurons that will integrate the neural network, specifically as inhibitory interneurons (periglomerular and granule cells). It could be shown that this process is increased after differential olfactory learning [3] and that the novel production (or the loss) of such interneurons has important consequences for OB activity. Structural plasticity is usually related to long-term forms of olfactory plasticity, as they need time to take place.

On a functional level, the strength and efficacy of synaptic transmission can be modified. This can imply many changes at the level of neurotransmitter release, receptor equipment, intra-cellular cascades, second messengers and for long-term forms, it relies on novel protein synthesis. Most functional work on olfactory plasticity has concentrated on describing changes observed in odor-evoked responses within olfactory structures. Depending on the recording technique, modifications are observed on the amplitude, frequency or synchronisation of electrophysiological responses [8,9], on the intensity or repartition of optically-monitored activity [4], on the pattern of production of synaptic proteins etc. In some experiments, plasticity is assessed on whole brain structures with awake and behaving animals. For instance, olfactory bulb field potential activity can be monitored from freely-behaving rats. Odor stimuli usually produce a frequency change in the ►field potential, with a power decrease in the γ frequency range (60–90 Hz) associated with a power increase in the β range (15–40 Hz). This pattern of response was found to be strongly amplified in animals trained in an olfactory learning task, precisely at the moment when they started mastering the task [9]. In such cases, it is difficult to determine precisely the location of this plasticity, which can reveal synaptic efficacy changes over a whole olfactory network. In other approaches, particular neuron populations can be monitored, usually in fixed animals. Thus, in rats, it could be shown in electrophysiological recordings of mitral cell activity that an olfactory exposure can modify their receptive range, so that they would respond to a wider range of odors after olfactory exposure than before [8]. In fruitflies, associative aversive conditioning based on odor-electric shock associations can be applied on a fixed fly under the microscope. Optical imaging experiments coupled to the genetic expression of a reporter of synaptic activity (synapto-PHluorin) in particular antennal lobe populations showed that projection neurons that were initially not activated by an odor prior to conditioning could be recruited shortly after differential aversive conditioning. Recordings from sensory neuron or inhibitory local interneuron populations did not show any change, demonstrating that plasticity took place at the level of second order neurons [10].

Until now, most available data on neural plasticity underlying olfactory learning was obtained from primary olfactory centers (OB/AL) that are easier to access. However, research on higher-order structures is growing. Thus, experiments have already shown that electrophysiological responses of neurons in the olfactory cortex are strongly influenced by previous odor stimulations, and are certainly involved in perceptual learning. But the kind of activity changes appearing at this level, in contrast to those found within the primary centers, correspond to higher-order computations allowing, for instance, the discrimination between a mixture and its components, a task deemed as one of the most critical for odor perception. Moreover, such higher-order structures are good candidates for harboring associative olfactory memories. In fruitflies, Kenyon cells (third order neurons) within the mushroom bodies displayed dramatic increases of calcium responses to the learned odor several hours after a differential aversive conditioning task, with even a localization of changes within specific branches of these neurons [10]. In fact, as only a few third order neurons are activated by a given odor, as opposed to many second-order neurons, neurons in more central areas constitute an ideal substrate for the associative memory trace, giving a particular odor a particular meaning.

Conclusion: Odor Processing Plasticity or Odor-Reinforcement Memory?

As detailed above, many electrophysiological, functional imaging or neuroanatomical studies find strong neural plasticity within olfactory circuits, especially after associative conditioning. However, it is often difficult to relate such neural plasticity to its exact function. Are the observed changes related to modifications of odor processing, modulating for instance the neural representation of the learned odors so that it can be better distinguished from environmental background? Or are they related to an olfactory ►engram,

revealing the storage of odor-reinforcement associations in the brain? The picture emerging from the studies carried out so far suggests that primary olfactory centers (OB/antennal lobe) may be responsible for the former, and higher olfactory centers for the latter, but considerable work is still needed to confirm this hypothesis. Future neurobiological studies of olfactory plasticity will have to answer these questions, using a combination of approaches, asking in particular whether the observed cells (and their plasticity) are necessary and sufficient for the expression of olfactory plasticity at the behavioral level.

References

1. Zufall F, Leinders-Zufall T (2000) The Cellular and molecular basis of odor adaptation. Chemical Senses 25:473–481
2. Herz RS (2002) Influences of odors on mood and affective cognition. In: Rouby C et al (eds) Olfaction, Taste and Cognition Cambridge University Press, UK, pp 160–177
3. Alonso M, Viollet C, Gabellec MM, Meas-Yedid V, Olivo-Marin JC, Lledo PM (2006) Olfactory discrimination learning increases the survival of adult-born neurons in the olfactory bulb J Neurosci 26:10508–10513
4. Faber T, Joerges J, Menzel R (1999) Associative learning modifies neural representations of odors in the insect brain. Nat Neurosci 2:74–78
5. Brennan PA, Keverne EB (1997) Neural mechanisms of mammalian olfactory learning Prog Neurobiol 51:457–481
6. Coureaud G, Moncomble AS, Montigny D, Dewas M, Perrier G, Schaal B (2006) A pheromone that rapidly promotes learning in the newborn. Curr Biol 16:1956–1961
7. Knafo F, Libersat F, Barkai E (2005) Dynamics of learning-induced spine redistribution along dendrites of pyramidal neurons in rats. Eur J Neurosci 21:927–935
8. Fletcher ML, Wilson DA (2003) Olfactory bulb mitral-tufted cell plasticity: odorant-specific tuning reflects previous odorant exposure. J Neurosci 23:6946–6955
9. Martin C, Gervais R, Hugues E, Messaoudi B, Ravel N (2004) Learning modulation of odor-induced oscillatory responses in the rat olfactory bulb: a correlate of odor recognition? J Neurosci 24:389–397
10. Berry J, Krause WC, Davis RL (2008) Chapter 18 Olfactory memory traces in Drosophila. Prog Brain Res 169:293–304

Olfactory Priming

►Olfactory Plasticity

Olfactory Receptor

Definition

Olfactory receptors are members of the seven transmembrane domain G-protein coupled family of receptor proteins. The binding of an odorant molecule to an olfactory receptor initiates a conformational change that activates the G-protein and leads to an electrical response in the olfactory sensory neuron that can be transmitted to the brain. Around 1,000 genes encoding functional olfactory receptor proteins have been identified in the mouse genome, with around 350 functional olfactory receptors identified in the human genome. Individual receptor types are typically activated by small and partially overlapping ranges of odorants. The identity of an odorant is therefore conveyed by the pattern of different odorant receptor types that it activates, i.e. an across-fiber pattern code.

►G-protein Coupled Receptors (GPCRs): Key Players in the Detection of Sensory and Cell-Cell Communication Messages
►Odorant
►Odorant Receptor
►Odor Coding
►Olfactory Sensory Neuron

Olfactory Receptor Neuron (ORN)

Definition

Olfactory receptor neurons are cells in the olfactory epithelium in the nasal cavity. They are bipolar neurons with an apical dendrite with cilia facing the interior space of the nasal cavity and a basal axon that via the first cranial (olfactory) nerve passes through the cribriform plate and enters the olfactory bulb. Each olfactory receptor neuron probably expresses a single type of olfactory receptor protein, and neurons with the same receptors are scattered through one of four zones in the epithelium. Olfactory sensory neurons are also sometimes called “olfactory receptors,” although this term can be confused with the odorant receptor proteins themselves. It should be noted that the olfactory epithelium is also innervated by the trigeminal nerve,

which is responsible for mechanical sensations (touch and pressure), as well as pain and temperature. Trigeminal fibers also respond to chemicals found in onions, mustard and chile powder.

►Odorant Receptor Protein
►Olfactory Bulb
►Olfactory Epithelium
►Olfactory Nerve

Olfactory Receptor Protein

►Odorant Receptor

Olfactory-recipient

Definition

Parts of the basal telencephalon receiving inputs from the main olfactory bulb. Olfactory-recipient areas include the olfactory amygdala and, depending on the species, the ventral telencephalon, lateral pallium, lateral cortex or olfactory cortex.

►Evolution of Olfactory and Vomeronasal Systems
►Olfactory Amygdala
►Olfactory Bulb
►Olfactory Cortex

Olfactory Recognition

Definition

Olfactory recognition, first and foremost, refers to the process by which an odor molecule is sensed and detected by an olfactory receptor. This process is not yet well understood, mainly because of the fact that the protein structure and function of many G-protein coupled receptors (GPCRs) is still under investigation. In contrast to most other GPCRs that recognize their ligands through ionic or hydrogen bond interactions, it appears that olfactory receptors recognize odorants primarily by weak hydrophobic and van der Waals interactions, which allow the observed broad but selective odor ligand binding of olfactory receptors.

►G-protein Coupled Receptors (GPCRs): Key Players in the Detection of Sensory and Cell-Cell Communication Messages
►Odor
►Odorant
►Odorant Receptor Protein
►Olfactory Receptor
►Olfactory Receptor Neuron

Olfactory Sense

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Synonyms

Sense of smell; Chemosensation; Odor perception

Definition

The olfactory system enables most animals to continuously monitor their chemical environment. The sensitivity and range of olfactory systems is remarkable, enabling organisms to detect and discriminate between thousands of low molecular mass, mostly organic compounds which we commonly call odors. The task is accomplished by specialized olfactory sensory neurons which encode the strength, duration and quality of odorant stimuli into distinct patterns of afferent neuronal signals. Thus, the molecular structure of an odorant molecule is converted into a pattern of electrical activity, which intern is processed in the olfactory bulb and higher brain centres and ultimately perceived as a characteristic odor quality. Odor perception is a result of complex biochemical and electrophysiological reaction mechanisms.

Characteristics

Measurable characteristics of olfaction are:

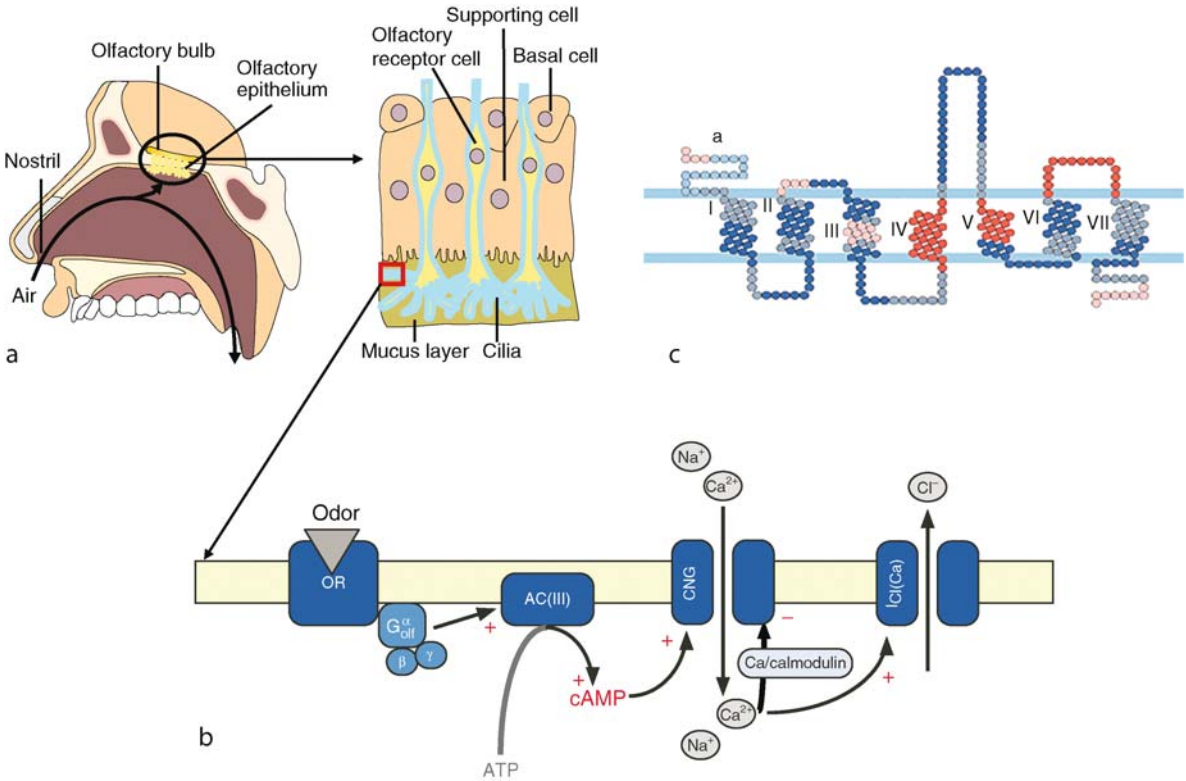
1. Anatomical organization
2. Signal transduction pathway (molecular basis of sensitivity and specificity)
3. Odorant information processing
4. Olfactory receptors outside the nose

The human nose is often considered something of a luxury. However, even if we have lost faith in our noses, we are still strongly influenced by smells even if only subconsciously. Smells can evoke memories and

emotions, influence our mood and are important for our enjoyment when eating. All the delicate nuances of an excellent cuisine or of a noble glass of wine are, in the final analysis, savored through our sense of smell. In addition, before the spirit and beauty of a person can fascinate us, our nose must become infatuated. The olfactory systems have developed, the main olfactory system (described here in detail) and the accessory system, known as the ►vomeronasal system (►Vomeronasal Organ (system)), which is specialized for chemical communication between one another (see glossary). An indication of the importance of the olfactory system in humans is the significant proportion – more than one percent – of the genome is devoted to encoding the proteins of smell. Let us follow the odor trail from molecule to perception.

Atomical Organization

A flower or any odorous subject has to release molecules according to their vapor pressure into the air. During inhalation they can reach our nasal cavity. There is a series of conchal formations, called turbinates. In the most upper one the olfactory epithelium is located, which consists of three mature cell types: bipolar primary sensory olfactory neurons, supporting (sustentacular) cells and basal cells (adult stem cells) which generate olfactory receptor neurons and sustentacular cells throughout our whole life (Fig. 1a). The turnover of the about 20 million olfactory neurons in less than one month. At the apical pole of the cell body of an olfactory sensory neuron (OSN) is a single dendrite that reaches up to the surface of the tissue and ends in a knob like swelling from which project some 20–25 very fine cilia. These cilia, which actually lie in the thin layer of mucus covering the tissue, contain all the molecular components necessary to convert the chemical odor stimulus into an electrical cell signal [1]. On the proximal pole the cell body of OSN narrows into an axon that joins with other axons to form small nerve bundles that then project into a region of the brain, known as the olfactory bulb. Molecular genetic studies have shown that all the neurons, expressing a particular olfactory receptor protein terminate within a single target in the olfactory bulb, called glomerulus: Spherical conglomerates of neuropil some 50–100 µm in diameter that consist of the incoming axons of OSN and the dendrites of the main projection cells in the bulb, the mitral cells. In human, as in other vertebrates, the number of glomeruli correlates with the number of different types of OSN (about 350).



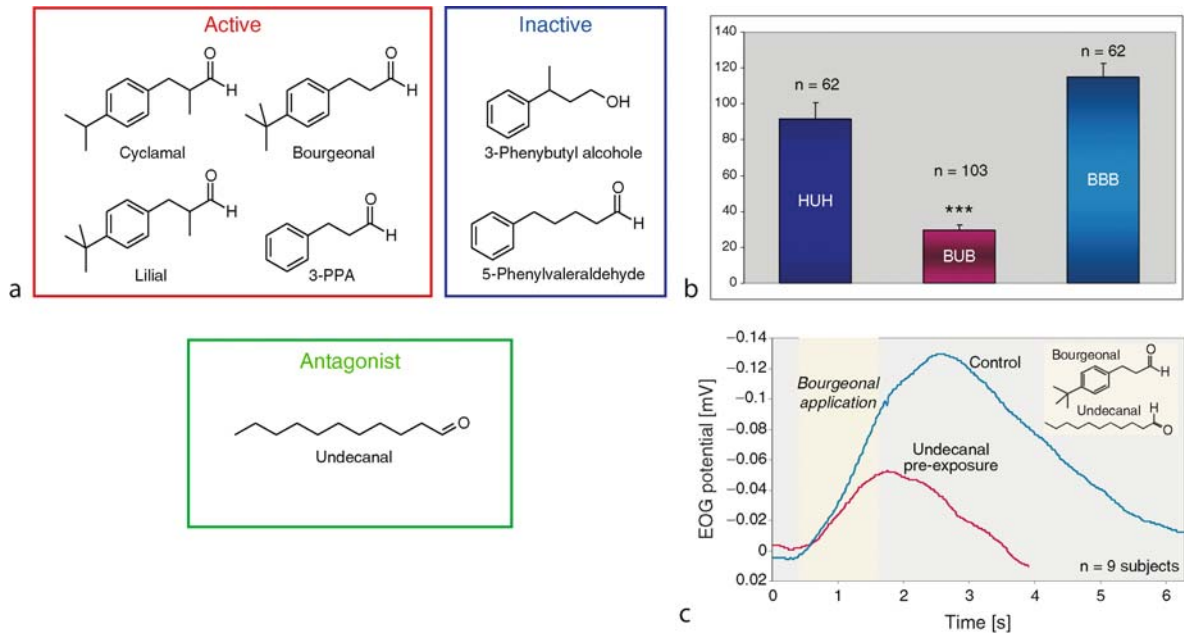
Olfactory Sense. Figure 1 (a) General layout of the nasal chemoreceptive area (*left side*) and the olfactory epithelium (*right side*). (b) Molecular processes during transduction of odor stimuli in an electrical cell response. (c) Molecular structure of a human olfactory receptor protein. The amino acid chain passes through the cell membrane seven times.

Signal Transduction Pathway

Recent advances of electrophysiological and molecular biological methods have provided new insights into the mechanisms of chemosensory signal transduction. The transduction process begins when odorants are dissolved in the mucus. Here the discovery of small, water soluble proteins in the mucus fluid, which are produced by glands of the nasal cavity, has led to the concept that these so-called odorant binding proteins (OBP) may accommodate hydrophobic odor molecules in an aqueous environment and enhance their access to the receptor sides. Several distinct OBP-subtypes have been identified and each subtype appears to have an unique ligand binding profile suggesting a more specific role of these proteins [1]. Meanwhile, it is generally accepted that the interaction of odor molecules with the receptor protein leads to the activation of a so-called ►G_{olf}-protein as mediator to activate the enzyme adenylate cyclase which produces large amounts of cyclic adenosine monophosphate (cAMP) as second messenger. The cAMP molecules now act directly within the cell membrane to change the structure (conformation) of a channel protein (cyclic nucleotide gate channel, CNG) in its open state (Fig. 1b), enabling it to conduct specific cations (Na^+, Ca^{2+}) from the nasal mucosa into the cell [2]. As a result, the negative membrane potential (about −70 mV at rest) is shifted to more positive values, called depolarization or cell excitation. Above a certain threshold (−50 mV) this analog sensor potential is converted into a digital action potential frequency near the axon hill of the soma of the OSN. The action potentials are conducted along the neurites into the olfactory bulb. This signal transduction cascade provides amplification and integration of odorant binding events. One olfactory receptor protein activated by an odor molecule can produce about a thousand molecules of a second messenger (cAMP) per second. The calcium ions entering through the CNG channel have a double function. First, they are able to activate another ion channel that is permeable to the negatively charged chloride ion [2]. Because OSN maintain an unusual high intracellular chloride concentration such that there is a chloride efflux when these channels are activated. Thus, it further depolarizes the cells and adding to the excitatory response magnitude. However, calcium ions entering the CNG-channels are also important in response adaptation through a negative feedback pathway. Calcium acts probably via a ►calmodulin dependent mechanism to decrease the affinity of the channel for cAMP and therefore making the channel after a longer period of opening more and more insensitive. This is one of several mechanisms for adaptation. Others include phosphorylation of olfactory receptor proteins sending them into ►internalization, and of fast sodium channels leading to inhibit of action potentials.

The initial step in the recognition of an odorant is its binding to the olfactory receptor protein. The discovery of a large family of genes which encode heptahelical transmembrane proteins (Fig. 1c) and are expressed exclusively in the olfactory epithelium by Linda Buck and Richard Axel (1991) was the ground-breaking work which opened new avenues of research for better understanding of odorant recognition [3]. The odorant receptor proteins are classical G-protein coupled receptors and the about 320 amino acids are highly homologous and Southern blots of genomic libraries suggested that the gene family consists in mice of at least 1,300 putative members. In the human genome about 900 olfactory receptor genes were identified, but two third of these turned out to be non-functional or "pseudogenes" which have lost their function during evolution. A total of 347 putative functional olfactory receptor genes in man was determined [4]. It is still the largest gene family in the human genome. The high proportion of pseudogenes indicate a variable repertoire of functional olfactory receptor genes in the human population. Many specific anosmia, e.g., the inability to smell particular odors, could be due to hereditary defects of OR genes. Interestingly, out of the 347 functional OR genes, each olfactory sensory cell expresses only one type which implies a sophisticated mechanism of olfactory gene choice. The members of the olfactory receptor gene family are distributed on nearly every human chromosome except 20 and Y, often found in large clusters. Chromosome 11 is particularly notable in that it contains nearly half of all olfactory receptor genes including the two largest olfactory receptor gene clusters [4].

In 1998, six years after its identification, it could be shown by functional expression and characterization of olfactory receptor genes that they encode for odorant receptors [5]. One year later the first human olfactory receptor was deorphanized. The receptor hOR17–40 reacts specifically to Helional and structurally related substances [6]. The functionality of the protein was demonstrated by a recombinant expression of the receptor in HEK 293 cells and calcium imaging measurement to demonstrate the cell response after odor application. Unfortunately, it has not been possible to get a functional expression and activation of many of the human olfactory receptors so far. The ability of olfactory sensory neurons to express cloned receptors while other cells could not is further evidence for the involvement of some olfactory specific ►chaperone or cofactor necessary for functional receptor expression. So only a few other human olfactory receptors have been successfully expressed and characterized. Most data existing from the receptor hOR17–4 which is activated by odorants like Bourgeonal, Cyclamal and Lilial (smelling like Lilly of the Valley). A detailed molecular receptive field (Fig. 2a) could be described [7]. From these data it was suggested that the receptor

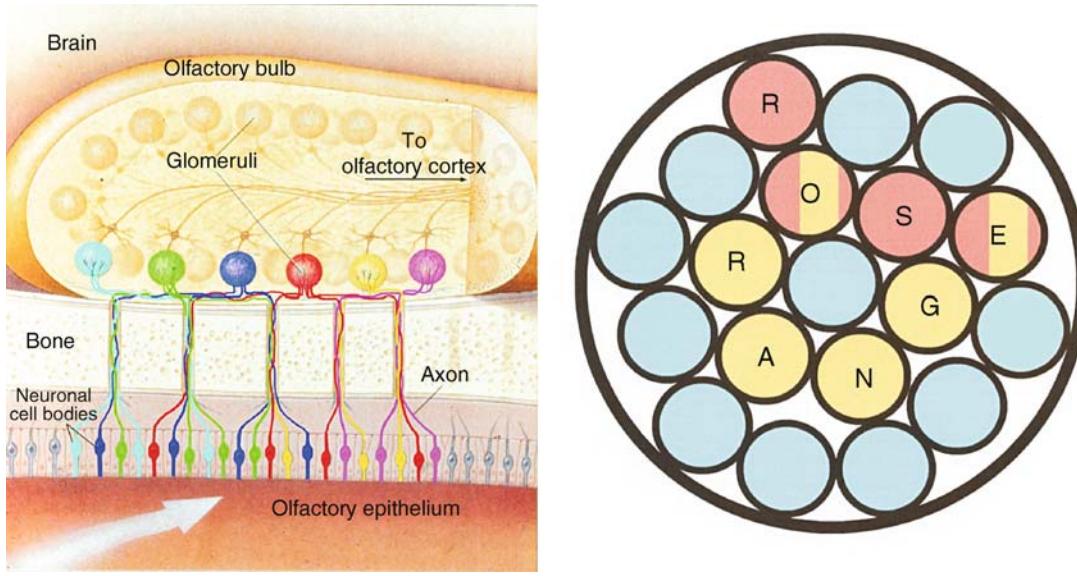


Olfactory Sense. Figure 2 (a) Effective versus ineffective agonists and antagonists towards hOR17–4. (b, c) In psychometric measurements and electro-olfactogram recordings Undecanal was identified as ►competitive antagonist for hOR17–4.

recognizes a particular feature of different ligands, in analogy to a ►pharmacophore in medical chemistry. In addition another analogy to pharmacology, the existence and the effectiveness of antagonists, could be shown. It was speculated for many years that it should be possible to construct antagonists for olfactory receptors in a similar way as in the case of the medically used blockers of adrenergic or dopaminergic receptors. Interestingly, under the many substances tested, Undecanal showed a clear competitive antagonistic effect highly specific for the receptor hOR17–4 [8]. Variations of agonist/antagonist concentrations ratios indicate competition of both compounds for the receptors ligand binding pocket (Fig. 2b, c). Most odor molecules are recognized by more than one receptor and most receptors recognize several odor molecules, related by chemical properties. Thus, the recognition of an odorant molecule depends on which receptors are activated and to what extent. For each odorant there are best receptors, but also others that are able to recognize the odorant only in a higher concentration and will participate in the discrimination of that compound. Thus, all data indicate that the nose uses a combinatory coding scheme to discriminate the waist number of different smells [4].

Odorant Information Process

To inform the brain, olfactory sensory neurons extend axons from the olfactory epithelium to the olfactory bulb. There is a considerable amount of data demonstrating that all neurons expressing the same receptor type convert their axons into the same glomerulus: usually two glomeruli which are located on the lateral and medial hemisphere of the bulb, respectively [4]. These findings indicate that an individual glomerulus is dedicated to receiving input from a single receptor type and so serves as a functional unit in the coding of olfactory information. The wiring process is still largely unknown. The basic olfactory map is probably established by a developmental hardwired strategy. The convergence of signals from thousands of neurons expressing the same olfactory receptor protein onto a few glomeruli by optimize the sensitivity to low concentrations of odorants by allowing the integration of weak signals from many olfactory epithelium neurons. The invariant pattern of inputs might have a different advantage, ensuring that the neuronal representation (code) from odorant remains constant over time, even though olfactory epithelium neurons are short lived cells that are continuously replaced. Many natural odors such as flowers, scents and perfumes consist of hundreds of individual chemical compounds. When such a complex mixture reaching our nasal cavity, out of the about 350 different types of olfactory sensory cells, only those are activated which bearing receptors for one of the chemicals in the mixture. Having in mind that all the sensory cells have the same receptor proteins, wherever they may be located in the olfactory epithelium (Fig. 3), all send their neuronal processes to one and the same glomerulus in the olfactory bulb, thus producing a

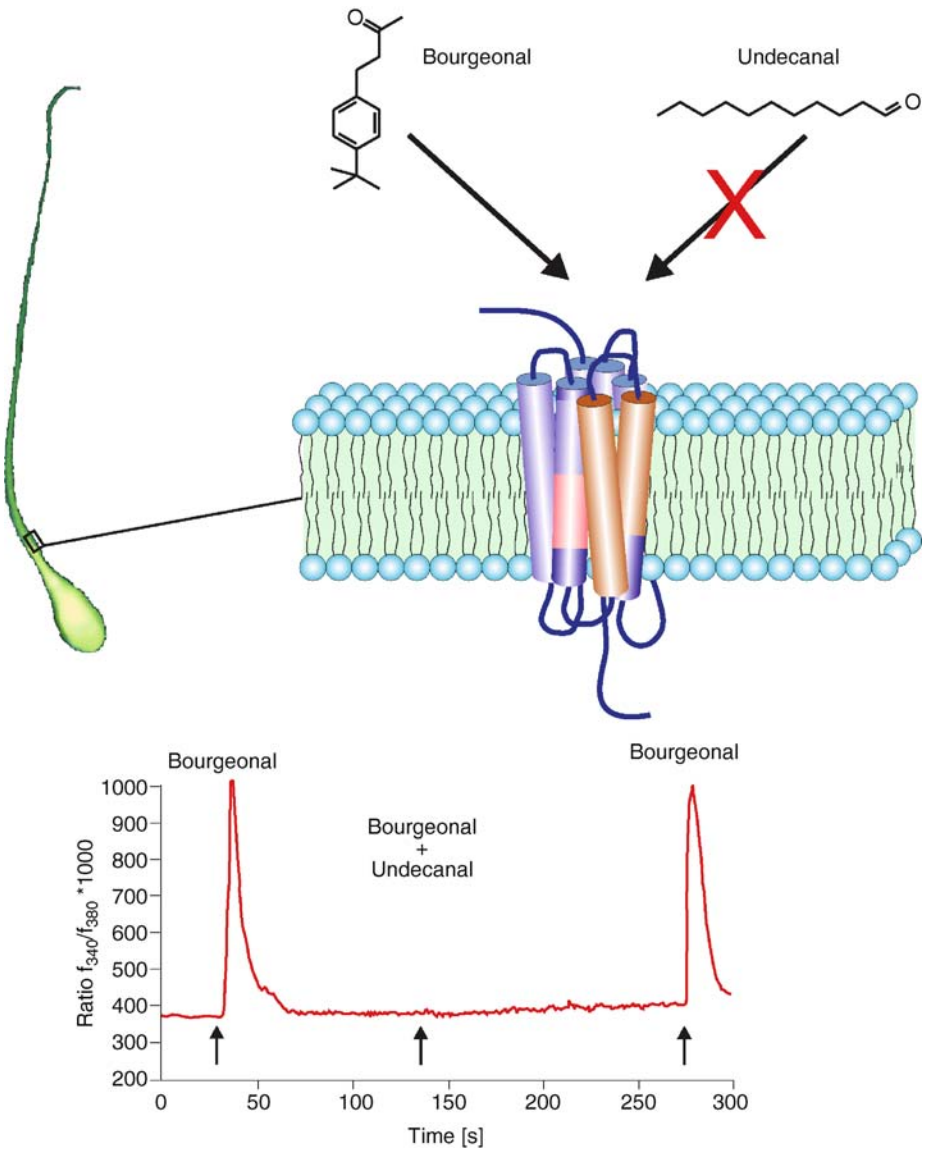


Olfactory Sense. Figure 3 (a) Olfactory receptor neurons expressing the same olfactory receptor protein project to a specific glomerulus in the olfactory bulb. (b) Schematic activation model of the glomeruli after stimulation with the scent of rose or orange.

constant activation pattern. For instance, when we smell the odor of a rose, the complex odorant mixture in a rose essential oil activates about hundred different receptor types and a similar number of glomeruli. The result is a reproducible, but complex pattern of glomerular activation, from which it is possible to interfere by reverse logic which odor mixture has been smelt [9]. The rose scent activation pattern is clearly distinct from e.g., an orange-scent pattern (Fig. 3). Although individual chemical components are present in both odor mixtures, the patterns in activated glomeruli can overlap but are clearly discriminable. In psychology, this representation by a particular shape could be described with the terms "Odor Gestalt" or "Gestalt Recognition." Once we have learned an odor, we can recognize it again, even though some of the information it normally contains may be missing. Many artificial rose or orange scents that are industrially produced take advantage of this knowledge.

Olfactory Receptors Outside the Nose

Recently it could be shown that olfactory receptors also exist and play an important functional role outside the olfactory epithelium: in human sperm cells. The latter possess olfactory receptor proteins as well as all the other members of the second messenger cascade, the G-protein, adenylate cyclase (Type III) and cyclic nucleotide gated channels [7,10]. Oversimplifying one could say that a sperm cell is nothing more than an olfactory neuron with a tail. Using molecular biological techniques (►Polymerase Chain Reaction (PCR)), biochemical methods (antibodies) and proteome analysis, it was clearly demonstrated that the receptor hOR17–4 is functionally expressed in human spermatozoa. By calcium imaging experiments it was shown that sperm cells indeed get activated by odorants like Bourgeonal or Cyclamal in a concentration dependent manner (Fig. 4). The threshold was in the micromolar range. Sperm react exactly to the same profile of active and inactive substances of the hOR17–4 as the recombinantly expressed receptor. Interestingly, the activation of hOR17–4 is completely inhibited by simultaneous presentation of the competitive inhibitor Undecanal [7]. These studies on the pharmacology of the sperm odorant receptor were then extended to the physiology of spermatozoa: Human sperm cells showed a concentration dependent positive chemotactic behavior to stimulating odorants (Bourgeonal, Cyclamal) and doubled their speed in presence of the odor. When the antagonist was applied, the effects of Bourgeonal on sperm navigation and swim speed were strongly inhibited. These data suggest that hOR17–4 signaling potentially governs chemical communication between sperm and egg cell. Additional studies made the important finding that this sperm receptor is in fact also expressed in human olfactory receptor neurons. Careful analysis of human tissue revealed bonafide expression of hOR17–4 in nasal epithelium [8]. The nose smells what sperm attracts. These data could potentially be used to manipulate fertilization with important consequences for contraception and procreation, but also to develop sniffing tests for identification of patients with fertilization problems based on functional olfactory receptors.



Olfactory Sense. Figure 4 Bourgeonal works as a potent receptor agonist of hOR17–4 in human spermatozoa, whereas Undecanal inhibits this effect.

References

1. Breer H (2003) Olfactory receptors: molecular basis for recognition and discrimination of odors. Anal Bioanal Chem 377:427–433
2. Frings S (2001) Chemoelectrical signal transduction in olfactory sensory neurons of air-breathing vertebrates. CMLS Cell Mol Life Sci 58:510–519
3. Buck L, Axel R (1991) A novel multigene family may encode odorant receptors: a molecular basis for odor recognition. Cell 65:175–187
4. Malnic B, Godfrey PA, Buck LB (2004) The human olfactory receptor gene family. Proc Natl Acad Sci USA 101:2584–2589
5. Firestein S (2001) How the olfactory system makes sense of scents. Nature 413:211–218
6. Wetzel ChH, Oles M, Wellerdieck Ch, Kuczkowiak M, Gisselmann G, Hatt H (1999) Specificity and sensitivity of a human olfactory receptor functionally expressed in human embryonic kidney 293 cells and *Xenopus laevis* oocytes. J Neurosci 19:7426–7433
7. Spehr M, Gisselmann G, Poplawski A, Riffell JA, Wetzel CH, Zimmer RK, Hatt H (2003) Identification of a testicular odorant receptor mediating human sperm chemotaxis. Science 299:2054–2058
8. Spehr M, Schwane K, Heilmann S, Gisselmann G, Hummel H, Hatt H (2004) Dual capacity of a human olfactory receptor. Curr Biol 14(19):832–833
9. Shepherd GM (2006) Smell images and the flavour system in the human brain. Nature 444:316–321
10. Weyand I, Godde M, Frings S, Weiner J, Müller F, Altenhofen W, Hatt H, Kaupp UB (1994) Cloning and functional expression of a cyclic-nucleotide-gated channel from mammalian sperm. Nature 368:859–863

Olfactory Sensitivity

►Olfactory Perception

Olfactory Sensory Neuron

Definition
►Olfactory Receptor Neuron

Olfactory Sulcus

Definition
The olfactory sulcus runs bilaterally along the orbital surface of the forebrain. It divides gyrus rectus from medial orbital gyrus. In the olfactory sulcus the olfactory peduncle runs from the olfactory bulb to the anterior perforated substance.

►Olfactory Bulb
►Olfactory Peduncle
►Olfactory Pathways

Olfactory System

Definition
Main chemosensory system in vertebrates. It is composed of an olfactory epithelium, located in the postero-dorsal nasal cavity, a main olfactory bulb and olfactory-recipient areas of the telencephalon. It is able to detect numerous odorants, mainly volatiles, present in the environment.

►Chemical Senses
►Evolution of Olfactory and Vomeronasal Systems
►Odorant
►Olfactory Bulb
►Olfactory Epithelium

Olfactory System Dynamics

►Olfactory Information

Olfactory Tract

Definition
Nerve fibers connecting the olfactory bulb to the olfactory cortex.

►Olfactory Bulb
►Olfactory Cortex
►Olfactory Pathways

Olfactory Transduction

Definition
Intracellular cascade of enzymes induced by the binding of odorants to odorant receptors. The interaction between an odorant and its cognate receptor induces a transduction pathway, involving the activation of specific Golf proteins, adenylate cyclase III, cyclic nucleotide-gated (CNG) and negatively charged chloride ion channels, providing amplification and integration of odor-binding events. This olfactory transduction ultimately transmits an electric signal to the central nervous system that results in a sensation of smell.

►Odorant
►Odorant Receptor

Olfactory Trigone

Definition
The olfactory trigone is a small portion of the olfactory peduncle. The olfactory peduncle runs from the olfactory bulb to the anterior perforated substance.

There, its diameter increases before it divides into three roots, or striae. This portion is termed olfactory trigone.

►Olfactory Bulb
►Olfactory Pathways
►Olfactory Peduncle

Olfactory Tubercle

Definition

From the olfactory trigone, the intermediate olfactory stria continues onto the anterior perforated substance. On top of the anterior perforated substance, there is a layer of gray matter, which is called the olfactory tubercle. In most mammals, the olfactory tubercle is a prominent bulge on the ventral surface of the frontal lobe situated caudally to the olfactory peduncle and medially to the lateral olfactory tract of mammals. It receives afferent input from the lateral olfactory tract. The olfactory tubercle differs from the piriform cortex in that it does not send output projections to the olfactory bulb or to any other secondary olfactory structure. The outputs of the olfactory tubercle are directed towards the thalamus, ventral pallidum, nucleus accumbens and, in monkeys, the orbitofrontal cortex. The inputs and projections to and from olfactory tubercle can vary substantially among species. The olfactory tubercle resembles the underlying corpus striatum and thus is often combined with the nucleus accumbens to the ventral striatum. In humans the olfactory tubercle is poorly developed resulting in a difficult visualization using functional imaging techniques.

►Olfactory Pathways
►Olfactory Tract
►Olfactory Trigone

Oligoclonal Bands (OCBs)

Definition

OCBs are distinct bands of IgG seen in electrophoretic analysis of CSF in MS patients. A few antibody-producing plasma cell clones produce the IgG within the CNS. This pattern is not normally seen since most IgG in CSF is derived from serum and appears as diffuse broad bands in CSF as well as in serum. In MS, two or more bands must be seen in CSF and be absent in serum indicating intrathecal synthesis of IgG. Though approximately 90% of CDMS patients have OCBs, they may also be found in patients with other CNS inflammatory or infectious diseases.

►Multiple Sclerosis

Oligodendrocyte

Definition

Oligodendrocytes are a type of glial cell in the CNS. The cytoplasmic extensions of these cells form myelin, which wraps around large axons. One oligodendrocyte can myelinate up to 30 axons. Oligodendrocytes are found predominantly in the white matter of the CNS. Diseases of oligodendrocytes include demyelinating diseases such as multiple sclerosis, leukodystrophies and tumors named as oligodendrogliomas.

►Inhibitory Molecules in Regeneration
►Multiple Sclerosis
►Myelin
►Regeneration

Oligodendrocyte-Myelin Glycoprotein (OMgp)

Definition

►Regeneration

Olivary Pretectal Nucleus

Definition

The olivary pretectal nucleus (OPN) is a midbrain structure that is part of the circuit mediating the pupillary light reflex. It receives direct retinal input, including inputs from melanopsin expressing retinal ganglion cells. The firing rate of OPN neurons is

directly related to the intensity of light stimulation on the retina and correspondingly to the degree of pupillary constriction.

►Neural Regulation of the Pupil
►Pupillary Light Reflex
►Retinal Ganglion Cells

Olive

Synonyms
►Oliva

Definition
- Inferior olive is the actual "olive" and is located directly beneath the pons, in the myelencephalon. This large nucleus plays a major role in movement coordination.
- Superior olive: nuclear conglomeration in the ►Mesencephalon, is a component of the auditory tract.

Olivocerebellothalamic Circuit

Definition
Neuronal circuit between the thalamus, the dentate nucleus of the cerebellum, and the inferior olivary nucleus.

►Essential Tremor

OMgp

Definition
OMgp stands for oligodendrocyte myelin glycoprotein. It is a glycosylphosphatidylinositol-anchored protein expressed mainly by oligodendrocytes in the central nervous system (CNS). It is found concentrated at nodes of Ranvier and plays a part in the control of myelination. Through its interaction with the Nogo receptor OMgp can cause growth cone collapse and inhibition of neurite outgrowth.

►Glial Scar
►Node of Ranvier
►Oligodendrocyte

Omnipause Neuron Area

Definition
A small region on the midline of the brainstem near the boundary of the pons and medulla. Neurons in this structure discharge at high tonic rates whenever an animal is fixating, but then turn off sharply and completely for saccades in all directions. These cells function as an inhibitory brake on other saccade-related cells in the saccadic system during fixation and help to prevent unwanted saccades from occurring.

►Omnipause Neuron
►Saccade, Saccadic Eye Movements

Omnipause Neurons

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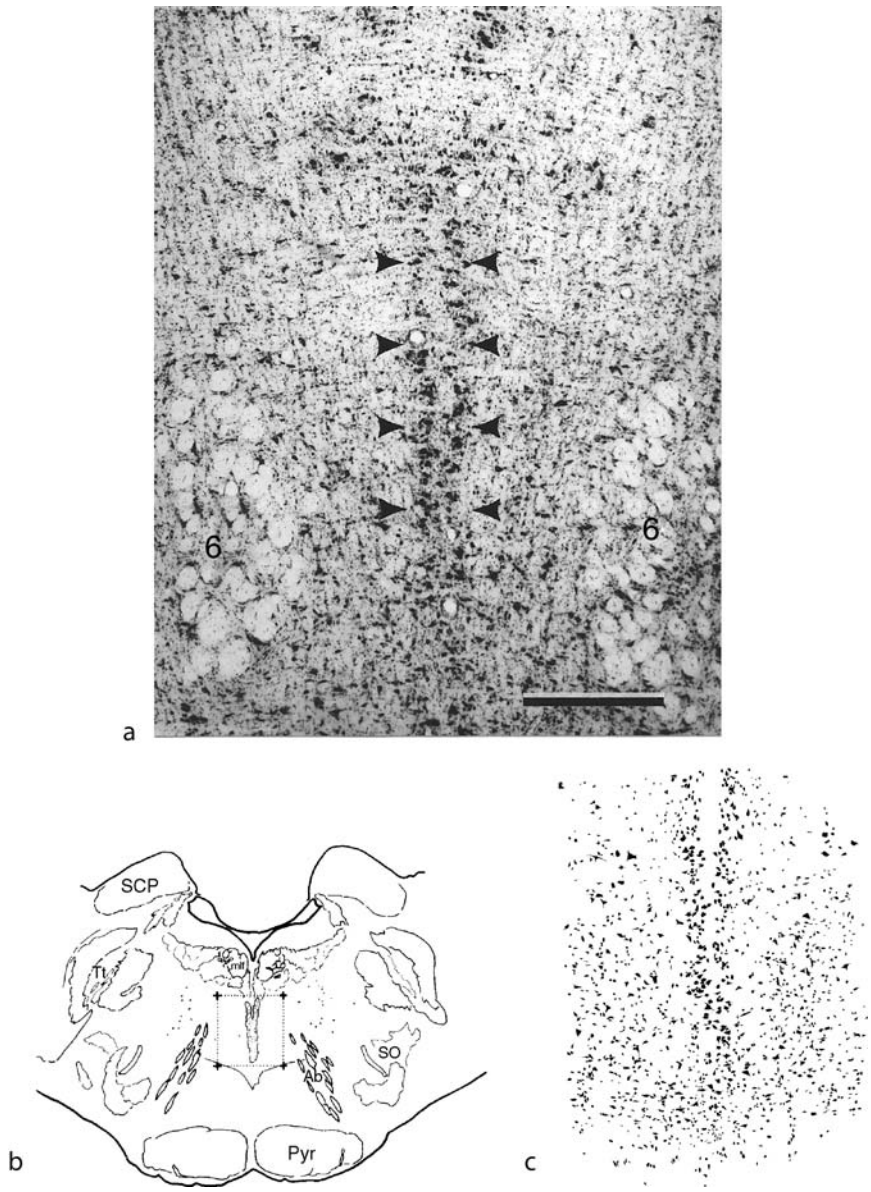
Synonyms
Pause neurons (pns); OPNs

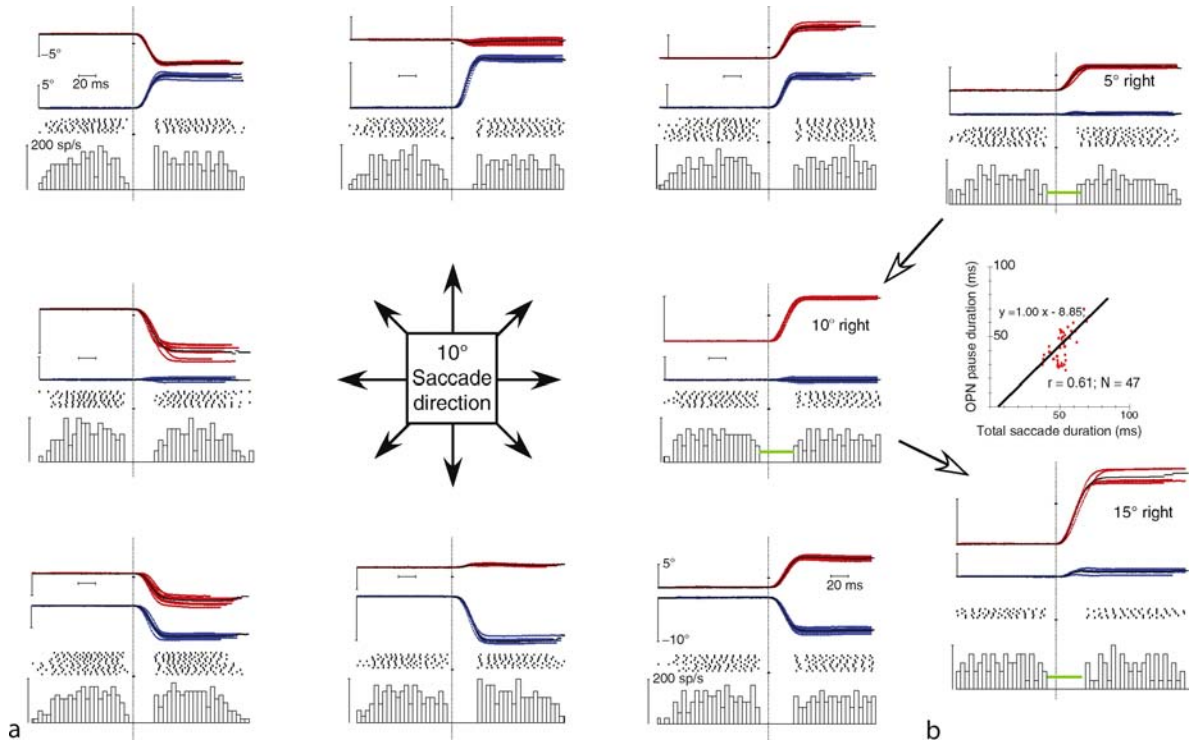
Definition
Omnipause neurons (OPNs) are the neurons that control saccadic eye movements by inhibiting the activity of all burst neurons. Burst neurons, in turn, directly drive the saccadic burst in motoneurons that produces the saccade. These neurons are located in the medial pons between the rootlets of the abducens nerves as they leave the brainstem ([4], Fig. 1). They are normally tonically active and discharge at a constant high rate (up to 200 ►spikes/s in ►rhesus monkey) that is unrelated to eye position (rasters and histogram, Fig. 2 bottom two traces in each panel). They cease firing (pause) before and during all saccades (Fig. 2). Their



Omnipause Neurons. Figure 1 OPN Anatomy. (a) Photomicrograph of the nucleus raphe interpositus (rip; arrowheads). OPNs are co-extensive with the rip and form a bilaminate columnar nucleus that straddles the midline between the rootlets of the abducens nerve [1]. (b) Tracing of the frontal section for orientation. The photomicrograph in (a) was taken from this section (dotted box). (c) Drawing of every neuron in (a) to show the distinct appearance of the OPNs is not due to poorly stained neurons, that the OPNs are larger than neighboring neurons, and are further distinguished by their isolated position between the longitudinal fiber tracks. Abbreviations: *6*, abducens nerve rootlets; *pyr*, pyramidal track; *SCP*, superior cerebellar peduncle. Calibration is 1 mm in (a).

pause begins just before (~15 ms) the onset (Fig. 2, thin vertical lines) of the movement and a few ms before the burst in medium lead burst neurons (mlbns). The duration of the pause is highly linearly correlated with saccade duration (Fig. 2b, middle). Anatomical studies have shown that OPNs project directly to both horizontal and vertical burst neuron regions. Physiological studies confirm that OPNs monosynaptically inhibit burst neurons. Based on their discharge and their connections, there is no doubt that OPNs control saccades by gating the activity of burst neurons.

OPNs are perhaps the most studied of the neurons that comprise the saccadic ▶burst generator, and saccades may be the best characterized motor system, so we know quite a bit about OPN anatomy and physiology. In 1972, Luschei and Fuchs [1] and Cohen



Omnipause Neurons. Figure 2 Discharge of OPNs. (a) In each panel, the traces are (top to bottom) horizontal eye position (red); vertical eye position (blue); rasters; histogram variability at ends is due to variable duration of each trace. 7–11 saccades in the direction indicated by the center plot are overlayed and the average (black line) shows the consistency of the movements. Note the pause lead. (b) Pause duration for different size saccades. 5° (upper) and 15° (lower) saccades show comparison of pause duration with 10° rightward saccades (indicated by green horizontal bar). Note the bar (redrawn) overlaps the pause for 5° and is shorter than that for 15° saccades. Traces as in (a). Middle, scatter plot of pause duration as a function of saccade duration for rightward saccades. Linear regression is least-squares fit to plot showing slope of one, i.e. pause duration equals saccade duration.

and Henn [2] reported recording eye movement related neurons in the pontine and medullary ►reticular formation of alert monkeys. One class, the OPNs, discharged at a high tonic rate (Fig. 2, rasters and histograms) but ceased firing in association with saccades or ►quick phases in any direction (Fig. 2a). Shortly thereafter, Keller [3] showed that electrical microstimulation of OPNs prohibited saccades and quick phases of ►nystagmus. This result immediately suggested their function was to control saccades by discharging at a high tonic rate in order to tonically inhibit burst neurons. These early results led to Robinson's model of saccadic control [4] that posited the role of OPNs was to prevent the discharge of the high gain, burst neurons that might otherwise cause instabilities in the system and thus, unwanted eye movements. He further suggested that saccades were initiated by a trigger signal of unknown origin mediated by an inhibitory interneuron and originating from more central structures like the superior colliculus. A final element was that the OPNs were modeled as being actively inhibited during the saccade to prevent unwanted interruptions of the saccade by means of a latch circuit comprised of burst neuron feedback to OPNs via another inhibitory interneuron.

While the basic circuit has been confirmed thoroughly in both cats and monkeys, some of the other details of the Robinson model [4] have garnered only rudimentary support. Anatomical tracing studies (e.g. [5]) showed that OPNs projected to each of the areas that contained saccadic burst neurons (see ►HMLBs (horizontal medium lead burst neurons), ►PPLLBs (ponto-pontine LLBs), ►PCbLLBs (precerebellar LLBs), and ►RSLLBs (reticulospinal LLBs)). Later, intracellular staining and modern tracing studies using transneuronal labeling have unequivocally demonstrated the projection from OPNs to burst neurons. Electrophysiological studies in cats have shown that this monosynaptic connection is inhibitory in all cases. Recent immunolabeling suggests that OPNs use glycine to inhibit burst neurons. Recordings from alert cats and monkeys and anatomical studies of their afferents has shown that the high rate of tonic discharge is probably due to a multiplicity of afferent input from all sensory modalities

[6]. This surmise is corroborated by the fact that OPNs are silent when animals go to sleep, and that a burst of OPN activity can be recorded if an afferent volley is synchronized by, for example, a click of sound. On the other hand, a neural basis for the trigger and the latch is yet to be established. Intracellular recording from identified cat OPNs has shown that they are inhibited during saccades. The inhibitory ►postsynaptic potentials (ipsps) are characterized by an initial abrupt hyperpolarization that decays back to resting, with a time course that is well correlated with saccadic eye velocity, consistent with them receiving both trigger and latch inputs. The ipsp decay is expected if it is caused by burst neuron input whose discharge is also highly correlated with eye velocity. Electrical microstimulation amongst long-lead burst neurons (LLBs) suggests some of them may be appropriate inhibitory interneurons to provide some of that input, but the juxtaposition of these elements has made it difficult technically to affect each element independently and thereby produce more substantive proof.

OPNs receive their major saccadic input from the contralateral superior colliculus. The input appears to be heavier from the caudal than the rostral portions of the colliculus and more concentrated from the lateral portions than the medial. The input is both monosynaptic (excitatory) and disynaptic (inhibitory), and it is assumed that the inhibitory input is relayed via an inhibitory interneuron and acts as a trigger for saccade generation. As mentioned, their high tonic rate is maintained by multiple afferent sources that use gamma-aminobutyric acid, glycine and glutamate but not monoamines as transmitters [7].

OPNs have been identified in man by immunohistochemistry and damage to OPNs has been invoked to explain a variety of eye movement pathologies, like square wave jerks, that result in oscillopsia. However, either transient or permanent inactivation of OPNs in monkeys leads to slower saccades (longer durations and lower peak velocities), possibly due to inactivation of ►post-inhibitory rebound in the EBNs that they innervate.

Characteristics

Higher Order Structures

There are three higher order structures that influence OPNs directly. OPNs receive input from the contralateral superior colliculus. Whether they also receive an ipsilateral input remains controversial. There also may be inputs from the frontal eye fields. One that projects directly to the pons, but this is still uncertain, and another that is indirect via the superior colliculus. Based on anatomical evidence, OPNs may also receive direct input from the caudal fastigial nucleus of the cerebellum that is presumably excitatory. The fastigial input may play a role in adaptive plasticity of saccade amplitude and/or saccadic error correction during on-going saccades by allowing fastigial output to terminate the saccade.

Parts of This Structure

OPNs have been studied extensively in cat and monkey and there are a number of differences between the species. The somata of the majority of OPNs (Fig. 1) are located in the nucleus raphe interpositus (rip) [8] in the monkey and in the nucleus raphe pontis in the cat [5]. In both species, occasional OPNs can be found in the surrounding reticular formation; specifically the caudal nucleus reticularis tegmenti pontis in the monkey [5] and the superior central nucleus in the cat. In the monkey, it appears that virtually all neurons in the rip are OPNs [5]. They are medium-sized (~35 μm diameter), multipolar neurons in monkey (Fig. 1a). In cat, their shape ranges from spindle shaped to spheroid and they are slightly larger (~46 μm, [9]). In monkey, OPNs send long horizontal dendrites in both directions, and the contralateral branches extend across the midline and into the longitudinal fiber tracts that traverse this portion of the pons in the ventral portion of, and below the medial longitudinal fasciculus. In contrast, cat OPN dendritic fields are ellipsoidal and only a minority have dendrites that cross the midline. Axons arise from the soma and bifurcate either ipsilaterally, or more usually, contralaterally after crossing the midline. In the cat, the stem axons are about 4 μm in diameter and the branch axons are about 3 μm in diameter. In the cases, from cat, where axons could be traced to terminal boutons, all were found in burst neuron regions and were either en passage or terminaux endings. The former were 2.6 μm in diameter and the latter 2.8 μm. Detailed intracellular fills are not available for monkey OPNs.

Function of This Structure

OPNs provide tonic inhibition to the saccadic burst neurons to prohibit saccades except when they are silenced. In addition, clinical and inactivation evidence suggests that the inhibition, when interrupted, contributes to activation of a post-inhibitory rebound in burst neurons that potentiates the very high-frequency discharge of burst neurons. Besides this permissive role in saccades, the OPNs also serve to coordinate various types of eye movements. The horizontal and vertical components of oblique saccades are mediated via separate horizontal and vertical burst neuron groups and are coordinated via OPN disinhibition. Thus, the OPNs serve to cross couple the burst neurons and control oblique saccade duration. This function is featured prominently in models of saccade generation that include both horizontal and vertical burst generators. The coordinating function seems to extend to other types of eye movements because OPNs are silenced during combined eye and head movements, combined ►vergence and ►version movements, as

well as during blinks. They may also have a role in slow pursuit eye movements, but the exact nature of that role is uncertain. Thus, OPNs seem to assist in the timing of coordinated eye movements in general.

Higher Order Function

OPNS are low-level premotor neurons with no higher order (e.g., cognitive) functions yet indicated. The function of the potential direct, cortical inputs is not clear, but all of the OPN inputs seem to share at least a portion of the responsibility for triggering saccades. Although still somewhat controversial, there don't appear to be any OPNs that are specialized either for head or coordinated eye and head movements, even though some LLBs are so specialized. As mentioned, their connectivity mediates the co-ordination of oblique saccades (►Hering's Law of equal innervation), and the push-pull organization of EBNs and IBNs results in relaxation of antagonist during agonist activation (►Sherrington's Law of reciprocal innervation). There is also emerging evidence that OPNs may play a role in the coordination of smooth pursuit and saccadic eye movements in both cats and monkeys, but the nature of that role has not yet been elucidated.

Quantitative Measure for This Structure

Just as for other elements of the saccadic burst generator, the number of OPNs is not clear because of technical limitations in marking all of them so that they may be counted. Perhaps transneuronal retrograde labeling techniques will allow an estimate in the near future. Likewise, virtually nothing is known about the unitary ipsps OPN output to burst neurons or the membrane biophysics of OPNs.

References

1. Luschei ES, Fuchs AF (1972) Activity of brain stem neurons during eye movements of alert monkeys. J Neurophysiol 35:445–461
2. Cohen B, Henn V (1972) Unit activity in the pontine reticular formation associated with eye movements. Brain Res 46:403–410
3. Keller EL (1974) Participation of medial pontine reticular formation in eye movement generation in monkey. J Neurophysiol 37:316–332
4. Robinson DA (1975) Oculomotor control signals. In: Lennerstrand G, Bach-y-Rita P (eds) Basic mechanisms of ocular motility and their clinical implication. Pergamon, Oxford, pp 337–374
5. Langer TP, Kaneko CRS (1990) Brainstem afferents to the oculomotor omnipause neurons in monkey. J Comp Neurol 295:413–427
6. Evinger C, Kaneko CRS, Fuchs AF (1982) Activity of omnipause neurons in alert cats during saccadic eye movements and visual stimuli. J Neurophysiol 47:827–844
7. Horn AKE, Büttner-Ennever JA, Wahle P, Reichenberger I (1994) Neurotransmitter profile of saccadic omnipause neurons in nucleus raphe interpositus. J Neurosci 14:2032–2046
8. Büttner-Ennever JA, Cohen B, Pause M, Fries W (l988) Raphe nucleus of the pons containing omnipause neurons of the oculomotor system in the monkey and its homologue in man. J Comp Neurol 267:307–332
9. Ohgaki T, Curthoys IS, Markham CH (1987) Anatomy of physiologically identified eye-movement-related pause neurons in the cat: Pontomedullary region J Comp Neurol 266:56–72

On Center Cells

Definition

►Visual Cortical and Subcortical Receptive Fields

Ongoing Neurogenesis

►Adult Neurogenesis

Oniric Mentation

►Dreaming

Ontogenetic

Definition

Pertaining to the biological development of an individual.

Ontological Status

Definition

Something's ontological status can be determined by answering the question whether it exists. Bill Clinton

and Sherlock Holmes, although both human beings, thus currently differ in ontological status.

►Logical

Ontology

Definition

Ontology is the study of being or of what there is. Typically, ontologies of philosophers might comprise concrete objects like chairs or electrons, abstract objects like numbers or ►propositions, properties like the property of being a chair, facts like the fact that Paris is west of Warsaw, or events like the 2004 World Series.

►Epiphenomenalism

Opacity

Definition

Primarily a feature of certain sentences, e.g., of many ascriptions of propositional attitudes. The truth of such ascriptions does not systematically depend on the truth or falsity of the proposition involved. Consider the following two belief-ascriptions: "Mary believes that 1 + 1 = 2" and "Mary believes that 2756 + 488 = 3244." Even though both propositions ("1 + 1 = 2" and "2756 + 488 = 3244") are true, the two beliefascriptions can differ in truth-value. Whether it is true that Mary believes that 2756 + 488 = 3244 therefore does not systematically depend on the truth of "2756 + 488 = 3244."

►Representation (Mental)

Open Loop Behavior

Definition

Behavior that is executed without feedback control. This may, in nature, be due to completing a task before feedback is possible.

Open Reading Frame

Definition

The region of the gene between the start and stop codon that encodes for the protein.

Operant

Definition

Control by the consequences, i.e. by positive or negative reinforcement (=punishment) that is the result of a particular behavior and that shapes the future expression of that behavior.

Operant Conditioning

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Synonyms

Instrumental conditioning

Definition

Operant conditioning describes a class of experiments in which an animal (including humans) learns about the consequences of its behavior and uses this knowledge to control its environment.

Characteristics

Our life consists of a series of experiences in which we learn about our environment and how to handle it. Learning about the environment ("the plate is hot") and learning the skills to control it ("riding a bike") have been experimentally conceptualized as classical and operant conditioning, respectively. The two are so intertwined that a treatment of operant conditioning is impossible without reference to classical conditioning.

Operant Conditioning

Operant (instrumental) conditioning [1] is the process by which we learn about the consequences of our actions, e.g., not to touch a hot plate. The most famous

operant conditioning experiment involves the "Skinner-Box" in which the psychologist B.F. Skinner trained rats to press a lever for a food reward. The animals were placed in the box and after some exploring would also press the lever, which would lead to food pellets being dispensed into the box. The animals quickly learned that they could control food delivery by pressing the lever. However, operant conditioning is not as simple as it first seems. For instance, when we touch a hot plate (or the rat the lever), we learn more about the hot plate than about our touch: we avoid contact of any body part with the plate, not only the hand that initially touched it. Obviously, we learned that the hot plate burns us. It is not only confusing that this type of environmental learning is usually called classical conditioning, we cannot even be sure that it is the only process taking place during conditioning.

Classical Conditioning

Classical (Pavlovian) conditioning [2] is the process by which we learn the relationship between events in our environment, e.g., that lightning always precedes thunder. The most famous classical conditioning experiment involves "Pavlov's dog": The physiologist I.P. Pavlov trained dogs to salivate in anticipation of food by repeatedly ringing a bell (conditioned stimulus, CS) before giving the animals food (unconditioned stimulus, US). Dogs naturally salivate to food. After a number of such presentations, the animals would salivate to the tone alone, indicating that they were expecting the food. The dog learns that the bell means food much as we learn that the plate is hot in the operant example above. Therefore, it is legitimate to ask if operant conditioning is in essence a classical process. Both operant and classical conditioning serve to be able to predict the occurrence of important events (such as food or danger). However, one of a number of important differences in particular suggests that completely different brain functions underlie the two processes. In classical conditioning, external stimuli control the behavior by triggering certain responses. In operant conditioning, the behavior controls the external events.

The Relationship Between Operant and Classical Conditioning

Ever since operant and classical conditioning were distinguished in 1928, their relationship has been under intense debate. The discussion has shifted among singular stimulus-response concepts, multiprocess views, and a variety of unified theories. Today, modern neuroscience distinguishes between procedural memories (skills and habits) and declarative memories (facts or events). The intensity and duration of the debate can in part be explained by the fact that most learning situations comprise operant and classical components to some extent: one or more initially neutral stimuli (CS), the animal's behavior (BH), and the ►reinforcer (US). The example above of learning to avoid touching a hot plate is very instructive. Extending the hand (BH) toward the round hotplate (CS) leads to the painful burn (US). In principle, our brain may store the situation as memory of the pain associated both with the hotplate (classical conditioning, CS-US) and with the extension of the hand (operant conditioning, BH-US) to predict the consequences of touching the plate at future encounters.

Habit Formation

A phenomenon called habit formation [3] confirms the tight interaction between operant and classical components in operant conditioning. In the early stages of an operant conditioning experiment (e.g., a rat pressing a lever for food in a Skinner box), the animal performs the lever presses spontaneously with the aim of obtaining the food (goal-directed actions). This can be shown by feeding the animals to satiety after training: they now press the lever less often when they are placed back in the box, because they are not hungry anymore. However, the same treatment fails to reduce lever pressing after the animals have been trained for an extended period. The behavior has now become habitual or compulsive; whenever the animals are placed now in the box, they frantically press the lever even if they are not hungry (or even if the food will make them sick). Although in the early stage of operant conditioning the behavior controls the environment (lever pressing to obtain food), habit formation effectively reverses the situation such that now the environment (box, lever) controls the behavior (lever pressing). One could say that overtraining an operant situation leads to a situation very similar to a classical one. Thus, operant conditioning consists not only of two components (operant and classical) but also of two phases (goal-directed and habitual behavior), with the relationship of the components changing with the progression from one phase to the next. Despite many decades of research filling bookshelves with psychological literature, our neurobiological understanding of the mechanisms underlying these processes is rather vague. What little is known comes from a number of different vertebrate and invertebrate model systems on various levels of operant conditioning. This essay is an attempt to integrate the neuroscience gained from many such disparate sources.

Neuroscientific Principles in Operant Conditioning

If there is a consensus for a critical early-stage process in operant conditioning, it is that of reafference. To detect the consequences of behavior, the brain has to compare its behavioral output with the incoming sensory stream and search for coincidences. The

neurobiological concept behind this process is that of corollary discharges (or efference copies). These efference copies are "copies" of the motor command sent to sensory processing stages for comparison. Thus, neurobiologically, any convergence site of operant behavior and the US is very interesting with regard to potential plasticity mechanisms in operant conditioning. The efference copies serve to distinguish incoming sensory signals into self-caused (reafferent) and other, ex-afferent signals [4]. Modern theories of operant conditioning incorporate and expand this reafference principle into two modules: one is concerned with generating variable behavior and another predicts and evaluates the consequences of this behavior and feeds back onto the initiation stage [5]. Some evidence exists that the circuits mediating these functions are contained within the dorsal and ventral striatum of the vertebrate brain. We have only very poor mechanistic knowledge about the first module. Behavioral variability could be generated actively by dedicated circuits in the brain or simply arise as a by-product of accumulated errors in an imperfectly wired brain (neural noise). Despite recent evidence supporting the neural control of behavioral variability, the question remains controversial. Only little more is known about the neurobiology of the second module. Promising potential mechanisms have been reported recently from humans, rats, crickets, and the marine snail *Aplysia*. These studies describe conceptually similar neural pathways for reafferent evaluation of behavioral output (via efference copies) and potential cellular mechanisms for the storage of the results of such evaluations at the convergence site of operant behavior and US. However, to this date, a general unifying principle such as that of synaptic plasticity in classical conditioning is still lacking.

From a larger perspective, there is evidence suggesting that the traditional distinction of entire learning experiments into either operant or classical conditioning needs to be reconsidered. Rather, it appears that an experimental separation of classical and operant components is essential for the study of associative learning. As outlined above, most associative learning situations comprise components of both behavioral (operant) and sensory (classical) predictors. Vertebrate research had already shown that operant and classical processes are probably mediated by different brain areas. Research primarily from the fruit fly *Drosophila* and *Aplysia* has succeeded in eliminating much if not all of the classical components in "pure" operant conditioning experiments, a feat which has so far proven difficult to accomplish in any modern vertebrate preparation. This type of operant conditioning appears more akin to habit formation and lacks an extended goal-directed phase. These paradigms successfully reduce the complexity of operant conditioning by isolating its components and as such are vital for the progress in this research area. The new invertebrate studies revealed that pure operant conditioning differs from classical conditioning not only on the neural, but also on the molecular level. Apparently, the acquisition of skills and habits, such as writing, driving a car, tying laces, or our going to bed rituals is not only processed by different brain structures than our explicit memories, but also the neurons use different biochemical processes to store these memories.

The realization that most learning situations consist of separable skill-learning and fact-learning components opens the possibility to observe the interactions between them during operant conditioning. For instance, the early, goal-directed phase is dominated by fact learning, which is facilitated by allowing a behavior to control the stimuli about which the animal learns. Skill learning in this phase is suppressed by the fact-learning mechanism. This insight supports early hypotheses about dominant classical components in operant conditioning [6], but only for the early, goal-directed phase. If training is extended, this suppression can be overcome and a habit can be formed. Organizing these processes in such a hierarchical way safeguards the organism against premature stereotypization of its behavioral repertoire and allows such behavioral stereotypes only if they provide a significant advantage. These results have drastic implications for all learning experiments: as soon as the behavior of the experimental subject has an effect on its subsequent stimulus situation, different processes seem to be at work than in experiments where the animal's behavior has no such consequences, even if the subject in both cases is required to learn only about external stimuli. Conversely, apparently similar procedural tasks that differ only in the degree of predictive stimuli present may actually rely on completely different molecular pathways. The hierarchical organization of classical and operant processes also explains why we sometimes have to train so hard to master certain skills and why it sometimes helps to shut out dominant visual stimuli by closing our eyes when we learn them.

References

1. Skinner BF (1938) The behavior of organisms. Appleton, New York
2. Pavlov IP (1927) Conditioned reflexes. Oxford University Press, Oxford
3. Yin HH, Knowlton BJ (2006) The role of the basal ganglia in habit formation. Nat Rev Neurosci 7:464–476
4. von Holst E, Mittelstaedt H (1950) Das Reafferenzprinzip. Wechselwirkungen zwischen Zentralnervensystem und Peripherie. Naturwissenschaften 37:464–476
5. Dayan P, Balleine BW (2002) Reward, motivation, and reinforcement learning. Neuron 36:285–298
6. Rescorla RA (1987) A Pavlovian analysis of goal-directed behavior. Am Psychol 42:119–129

Operant Conditioning

Definition

A Definition of operant conditioning, also called instrumental conditioning, requires a distinction between elicited and emitted behavior. Elicited behavior is a response that is associated with a biologically relevant stimulus. Pavlovian or classical conditioning is an example of elicited behavior since there is always a formal, temporal relationship between the conditional stimulus (for example, a bell) and the unconditional stimulus (for example, meat powder to the tongue which elicits salivation). After a number of pairings, the conditional signal is seen to elicit a response that is similar to that elicited by the unconditional stimulus. Emitted behavior is behavior, which is produced by the subject in order to obtain a desirable outcome (commonly called a reinforcer): such behavior is said to operate upon the environment to produce reinforcement. In typical studies of operant conditioning, the availability of the reinforcer is signaled by a cue of some sort. Thus, the relationship between elicited and emitted behavior is complex. However, any discussion of this issue goes well beyond the subject matter of this essay.

Operational Closure

Definition

Operational (or organizational) closure means that certain relations and processes define a system as a unity, in determining the dynamics of interaction and transformations that the system may undergo as such a unity (Maturana/Varela). Operationally closed systems are not causally closed, i.e. they may interact causally with the environment.

Operculum

Definition

Part of the posterior portion of the inferior frontal gyrus of the frontal lobe in the brain.

Ophiid (Type)

Definition

"Snake-like," "snake-type."

►Evolution of the Brain: At the Reptile-Bird Transition

Opioid

Definition

Any compound or substance that binds to the opioid receptor resulting in the activation of the receptor.

►Analgesia

Opioid Peptides

Definition

Opioid peptides are short sequences of amino acids which mimic the effect of opiates in the brain. Endogenous opioid peptides are derived from three gene families, β-endorphins, enkephalins and dynorphins. Three types of opioid receptors, μ, δ and κ receptors, are pharmacologically identified.

Opisthotonus

Definition

Arched back produced by tonic contractions of the back muscles, for example in ►tetanus.

►Tetanus (Pathological)

OPN4

►Melanopsin

OPNs

►Omnipause Neurons

Opsin Evolution

►Evolution of Eyes

Opsonin

Definition

A terminology derived from the Greek and meaning, sauce or seasoning, in other words making the target cells such as pathogen more palatable to the phagocyte and more easily eaten. For example, C3b is an opsonin bound to target cells following complement activation and promoting phagocytosis by macrophages expressing C3 receptors.

►Neurodegeneration and Neuroprotection – Innate Immune Response

Optic Ataxia

Definition

Specific impairment of the visual control of limb movements observed in patients with lesion of the posterior parietal cortex. This deficit is expressed as errors both in final limb position in reaching/pointing tasks and in the shaping of hand aperture in grasping tasks. These deficits are exacerbated when the movements are programmed and executed under peripheral vision by asking the patient to keep gaze on a fixation point. Pure forms of optic ataxia, without sensory or motor deficits, indicate a role of the posterior parietal cortex in visuo-motor transformations for limb movement control.

►Eye-Hand Coordination
►Visual Neurosychology
►Visual Space Representation for Reaching

Optic Axis

Definition

Where we look, i.e., roughly coincidental with the line of sight.

Optic Chiasm

Definition

The optic chiasm is a landmark between the optic nerve and optic tract in the pathway between the retina and lateral geniculate nucleus of the thalamus. It contains the crossing of fibers of the so-called optic nerve to form its continuation, the optic tract of the opposite side. The fibers arise from ganglion cells in the retina. The crossing fibers in the optic chiasm contain information from the temporal visual fields (retinal nasal fields) of both eyes. Uncrossed fibers in the optic chiasm contain information from the nasal visual fields (temporal retinal fields) of both eyes. The chiasm is located on the ventral surface of the brain at the level of the anterior hypothalamus.

Optic Flow

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Synonyms

Optical flow; (optic) Flow field; Retinal flow

Definition

Optic flow is the pattern of motion induced on the retina of a moving observer.

Characteristics

Mathematical Properties

Optic flow arises from the movement of an observer through a static visual scene. The movement of the observer creates relative movement between the visual objects in the scene and the eye of the observer. The projection of the relative movement of the scene objects

onto the ►visual field of the observer creates ►visual motion. The collection of all the visual motions from throughout the visual field forms the optic flow. Since the motion in the visual field is first sensed by its projection on the retina, retinal flow is the collection of all image motion on the retina that arises from observer movement.

The retinal projection of the relative movement of a point in the scene can be described as a motion *vector*, i.e., by noting the motion direction and speed on the retina. The direction depends on the particular self-motion that the observer performs. When the observer moves to the left, all image motion is directed to the right. When the observer moves straight forward, all image motion is directed radially away from a point in the movement direction of the observer. This point is known as the ►focus of expansion. The speed of a particular motion vector in the optic flow depends on the distance of the point from the eye of the observer. Points near to the observer move faster in the retinal projection than points further away. The difference in the speeds of two points in the same visual direction but in different distances from the observer is known as ►motion parallax.

Optic flow not only arises from linear translations of the observer, such as sideward or forward movement, but also from rotations. Such rotations can occur either from moving along a curve or from eye movements of the observer. For example, when the observer performs an eye movement from right to left then rightward visual motion is induced on the retina. However, unlike in the case of leftward linear translation, the speeds of the motion vectors induced by eye rotation do not depend on the distance of the respective scene points from the observer. All points move with the same speed which is exactly opposite to the speed of the eye movement.

Thus, a single optic flow vector θ of a point R in the scene is mathematically a function of the translation T and rotation Ω of the eye of the observer and the distance Z of the point from the eye: $\theta = f(T, \Omega, Z)$. The precise equation is derived from perspective geometry [1]. Important for many aspect of flow analysis is the fact that in this equation the observer speed T and the depth Z are coupled such that the flow depends only on the quotient T/Z, not on Z directly.

The simplest optic flow is that of the radial outward movement obtained from linear forward movement. However, this is only a special case and the combination of translation, rotation, and scene distances can give rise to very different optic flow patterns. Since observer movement naturally triggers gaze stabilization reflexes such as the ►vestibulo-ocular reflex or the ►optokinetic reflex the optic flow observed under natural conditions will often result from a combination of translation and eye rotation.

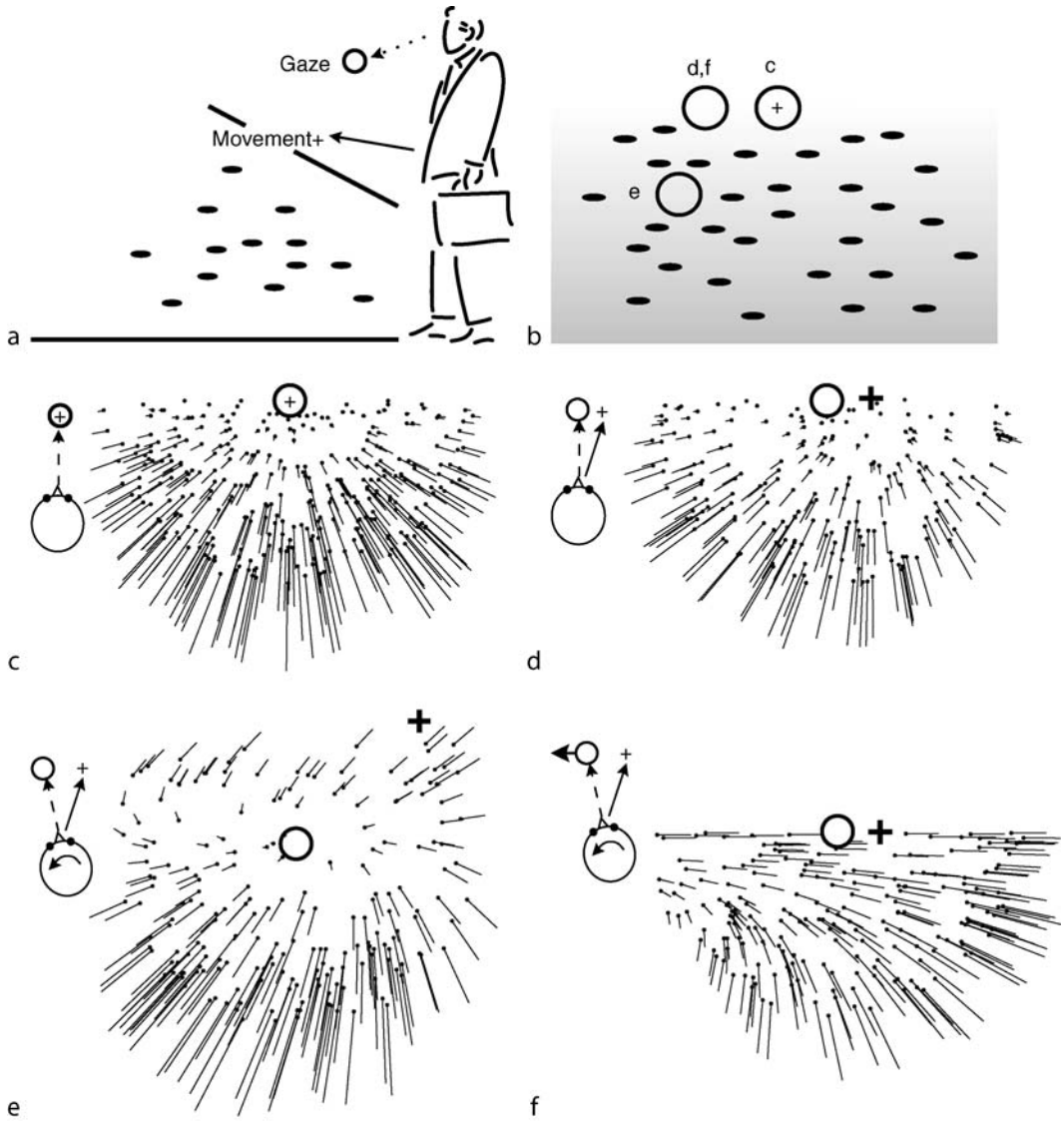
Figure 1 shows a few characteristic examples. The observer moves across a ground plane. Heading is marked by a cross, gaze direction by a circle. Panels c to f show cases where the same heading is combined with different gaze directions. These gaze directions are shown in panel b. Panel c shows the retinal flow when gaze coincides with heading, i.e., when the observer looks straight into the direction of movement. In this case a focus of expansion is centered on the retina. In panel d, the observer looks off to the side. Gazing at some fixed point on the horizon allows him to keep his eyes stationary, i.e., no eye movements occur. A focus of expansion identifies heading, but now it is displaced from the center of the visual field. In panel e, the observer's gaze is directed at some element of the ground located in front of him and to the right. Because gaze is directed downward the horizon is in the upper visual field. Moreover, since the observer now looks at a point that is moving relative to himself, an eye movement is induced to stabilize gaze on this point. The resulting retinal flow field, a combination of translational and rotational flow, resembles a distorted spiraling motion around the fovea. There is no focus of expansion in the direction of heading (+). In panel f the observer looks at the same point as in panel d, but now he tracks an object that moves leftward along the horizon (for instance a car). This leftward pursuit induces rightward retinal image motion. The combination with the forward movement results in a motion pattern that resembles a curved movement and does not contain a focus of expansion.

Behavioral Aspects

From its conception by Gibson in the 1950s [3] optic flow has been assumed to play a role in the control of self-motion. Since then, experimental studies have shown that optic flow is involved in many behavioral tasks:

Control of Stance. Direction and speed of the optic flow are used as feedback signals for postural stability. When standing observers are exposed to a large flow field that periodically expands and contracts they sway in phase with the flow field [4]. The coupling between optic flow and posture maintenance is particularly strong in children and decreases in strength with age as the influence of ►vestibular and somatosensory contributions to postural stability increases.

Control of Speed. Walking observers use the speed of the optic flow as a control signal for walking speed. Normally, a particular forward movement leads to a particular optic flow speed. If the flow speed is artificially increased, as has been done for observers walking on a treadmill in front of a projection screen on which a flow pattern was presented, walking speed increased proportionally [5]. Similar effects are seen for bicycling and car driving. When a mismatch between flow speed and walking speed is maintained for a



Optic Flow. Figure 1 Examples of optic flow fields induced by combinations of forward movement and eye movement. Taken with modifications from [2]. See text for detailed explanation. (a) Observer moves towards the cross while lookins at the circle. (b) different directions of gaze used in panels c to f. (c) Optic flow for straight translation int the direction of gaze. (d) Optic flow when directon of motion differs from direction of gaze. (e) Optic flow when direction of motion differs from direction of gaze and gaze stabilizing eye movement reflexes are taken into account. (f) Optic flow when direction of motion differs from direction of gaze and the observer tracks a moving object.

several minutes, for example when the flow speed is constantly lower than normal for a runner on a treadmill, an after effect is observed in which the walker inadvertently advances when attempting to run in place on solid ground with eyes closed.

3D Scene Perception. Because of motion parallax the optic flow contains information about the distances of the points of the scene. This information can be extracted to estimate the relative distances between objects in the scene and to recover surface layout [1]. Absolute distances cannot be retrieved from the optic flow because flow magnitude depends on the quotient of observer speed (T) and point distance (Z). For example, in an airplane flying high above the ground optic flow speed is very low even for very high forward speed of the plane. Thus, distance can only be calculated when the observer speed is known, which is usually not the case.

►*Time-to-Contact*. Information in the optic flow allows to estimate the time-to-contact or the time-to-passage with an obstacle during forward motion. By itself, the speed of an optic flow vector of a particular

object is insufficient for the estimation of distance to the object (because it depends on T/Z) but a combination of speed with object size or of speed with the object's visual angle allows a direct calculation of time-to-contact. This information may be used to control braking or catching and to control running speed and direction for the intersection with a target object (for instance in ball sports). An overview can be found in [6].

►*Path Integration*. By integrating the speed of the optic flow over time an estimate of the travel distance or path length of an extended movement can be obtained. This estimate is subject to a scale factor since the speed of the flow depends on both the speed of the self-movement and the distance to the objects in the environment, but in many natural circumstances the height of the observer above the ground can provide the required scale. The estimation of travel distance from optic flow is based on an the integration of an estimate of observer velocity that is derived from the optic flow [7].

Heading. Heading refers to the direction of the movement of the observer. Gibson's original proposal for the use of optic flow was the identification of the heading (for example when landing an aircraft) by locating the focus of expansion in the flow field. Most optic flow research since then has centered on heading perception (overviews in [8] and [9]). Indeed, human observers are quite accurate in finding the focus of expansion in an expanding flow field. However, the situation is much more complicated because in most natural situations the optic flow on the retina is influenced by rotations and the flow field does not contain a focus of expansion (cf. Fig. 1). Yet, geometric calculations prove that the optic flow in these cases also contains sufficient information to separate the translational and rotational contributions if several flow vectors are available [1]. Many computational algorithms have been developed for this task, among them a few that are formulated as biologically plausible neurocomputational models (overview in [2]). Human observers can indeed estimate heading from flow fields of translation and rotation with reasonable accuracy (a few degrees of visual angle). An important finding was that heading estimation can be performed solely from the information in the flow field, i.e., from the direction and speed of the flow vectors, without any other sensory signals necessary. However, in natural situations eye movements that influence the structure of the retinal flow are accompanied by extra-retinal eye movement signals such as the ►efference copy signal or eye muscle ►proprioception. These signals are also used in optic flow analysis and increase the accuracy of the heading estimate. Rotational contributions to the retinal flow may also arise from movements on a curved path, in addition to, or instead of eye movements. Therefore, a separation of translational and rotational contributions may only provide the momentary or instantaneous heading but not the full information about the future path of the observer, since the rotational contributions are ambiguous. Estimations of path curvature, which are required for steering for instance, can be derived from successive independent heading estimates or from a combination of optic flow and extraretinal eye movement signals. Alternatively, specialized behavioral strategies, such as fixating a specific point in the flow field, may allow the estimation of steering-relevant information directly from the retinal velocities.

Although the above descriptions refer to human observers, optic flow is used for such behavioral tasks throughout the animal kingdom (see [2] for several examples). The use of optic flow for the control of speed, distance, time-to-contact, and course control has been shown in insects, birds, and mammals, exemplifying the ecological importance of optic flow. Moreover, the above descriptions show that optic flow is often part of multi-modal mechanisms for behavioral control, interacting with ►proprioceptive, vestibular, and internal feedback signals. Exposure to optic flow is also known to induce ►vection, the subjective feeling of self-movement in a physically static observer.

Neurophysiological Processing

In the visual system of primates visual motion information is routed via V1 and V2 to the ►middle temporal (MT) and subsequently to the ►medial superior temporal area (area MST) and other visual areas in the parietal lobe. Most clearly related to optic flow is area MST (detailed reviews in [2]). Many neurons in area MST respond selectively to entire optic flow patterns and not just to an individual motion vector in a particular flow field. A neuron might respond selectively to a particular flow pattern, such as an expansion as in Fig. 1c, but when tested with small stimuli the selectivities in subfields of the ►receptive field do not match one-to-one the pattern of the preferred large flow field. Thus, MST neurons are genuinely selective for optic flow. Their selectivity arises from complex interactions between selectivities in local subfields. Functional ►brain imaging in humans has confirmed an area selective for optic flow which is part of the human ►MT± complex.

When tested with multiple different flow patterns such as visual expansions, rotations and translations, MST reveals a continuum of response selectivities. Some neurons respond to several different patterns or to flow fields that combine translational and rotational contributions. Instead of classifying the selectivity of MST neurons by the preferred pattern of flow it is also possible to describe their selectivity in terms of heading. Indeed, it is possible to calculate heading from the firing rates of the neuronal population in MST. Next to visual motion signals, area MST also receives extra-retinal eye movement information. This information is used to counteract the effects of eye movements on the retinal

flow and maintain selectivity for heading in the presence of eye movements. There are also interactions with vestibular signals during self-motion.

Other areas of the parietal lobe, the ►ventral intraparietal area (VIP) and area 7A, as well as the ►fundus of the superior temporal sulcus (FST) also respond to optic flow. Neurons in area MT, the major input to area MST, respond to optic flow but their responses can be explained by their selectivity to local image motion within their receptive field. However, some global properties of the visual field map in MT seem related to optic flow analysis. Preferred speeds increase with eccentricity similar to the increase of speed with eccentricity in typical flow fields. The distribution of preferred directions for neurons with peripheral receptive fields is biased towards centrifugal motion similar to the radial motion directions in a typical optic flow. The increase of the receptive field sizes with eccentricity is well adapted to the size of image patches over which neighboring flow signals are uniform. These patches are small in the center of the visual field, where optic flow vectors point in different directions, and large in the peripheral visual field where neighboring flow vectors are usually very similar. Computational modeling shows that this adaptation of receptive field sizes leads to significant noise reduction in the optic flow representation in area MT.

As mentioned above, optic flow is used by many animals. A brief description of the neuronal pathways of optic flow analysis in birds can be found in the essay on *visual-vestibular interactions*. In flies, optic flow is analyzed by a small number of neurons of the horizontal (HS) and the vertical (VS) system in the lobula plate (Krapp in [2]). Unlike neurons of primate MST, which show no simple correlation between local motion selectivities and flow patterns selectivity, the flow selectivity of these neurons in the fly is matched by the sensitivity to local motion in subfields of their very large receptive fields. These neurons seem to form matched filters for particular flow patterns. Like in primate MST, information about the translation and rotation of the animal can be decoded from the population activity.

References

1. Longuet-Higgins HC, Prazdny K (1980) The interpretation of a moving retinal image. Proc Roy Soc Lond B 208:385–397
2. Lappe M (ed) (2002) Neuronal processing of optic flow. International Review of Neurobiology, vol 44. Academic Press, New York
3. Gibson JJ (1950) The perception of the visual world. Houghton Mifflin, Boston
4. Lee DN, Aronson E (1974) Visual proprioceptive control of standing in human infants. Percept Psychophys 15:529–532
5. Prokop T, Schubert M, Berger W (1997) Visual influence on human locomotion – modulation to changes in optic flow. Exp Brain Res 114:63–70
6. Hecht H, Savelsbergh GJP (eds) (2004) Time-to-contact. Advances in Psychology, vol 135. Elsevier, Amsterdam
7. Frenz H, Bremmer F, Lappe M (2003) Discrimination of travel distances from 'situated' optic flow. Vision Res 43:2173–2183
8. Warren WH Jr (1998) Visually controlled locomotion: 40 years later. Ecol Psychol 10:177–219
9. Lappe M, Bremmer F, van den Berg AV (1999) Perception of self-motion from visual flow. Trends Cogn Sci 3:329–336

Optic Flow Dependent OFR

Definition

►Ocular Following Responses (OFR).

►Oculomotor Control
►Optic Flow

Optic Nerve

Definition

The optic nerve is the portion of the visual pathway between the retina and lateral geniculate nucleus of the thalamus that lays rostral to the optic chiasm. The continuation of the path caudally is the optic tract. The cell body of origin for this pathway is the ganglion cell in the retina.

Optic Neuritis

Definition

Sudden inflammation of the ►optic nerve occurring most often between 20 and 40 years of age, and may be a ►demyelinating disease of unknown origin or a co-manifestation of ►multiple sclerosis. The inflammation may occasionally be the result of a viral infection.

►Multiple Sclerosis

Optic Radiation

Synonyms
Radiatio optica

Definition
The visual radiation is the term used to designate the ray-shaped fiber bundles that leave the lateral geniculate body and at the lateral wall of the lateral ventricle pass on to the area 17 (striate cortex) at the occipital pole. They conduct the visual raw material after being processed by the LGB. Also called geniculocalcarine tract.

►Geniculo-striate Pathway
►Lateral Geniculate Nucleus (LGN)
►Primary Visual Cortex
►Striate Cortex Functions

Optic Tract

Definition
The optic tract is the portion of the visual pathway between the retina and lateral geniculate nucleus of the thalamus that lies caudal to the optic chiasm. The portion that is rostral to the optic chiasm is the optic tract. The cell body of origin for this pathway is the ganglion cell in the retina.

Optic Tract Nucleus

Synonyms
►Nucl. tractus optici; ►Nucleus of optic tract

Definition
The optic tract nucleus lies in the Myelencephalon near the superior colliculus. The nucleus is fused with the dorsal terminal nucleus and is an important center of the subcortical pathway which mediates horizontal optokinetic nystag

►Diencephalon

Optical Coherence Tomography (OCT)

Definition
OCT is an emerging ocular imaging technique to measure optic structures with micrometer resolution. It is useful in the measurement of retinal nerve fiber layer (RNFL) thickness and total macular volume corresponding to the ganglion cell body layer. The thickness of these unmyelinated nerve fiber layers may reflect axonal integrity, and function (vision) may be directly correlated with structure. Though RNFL thickness may be significantly decreased in multiple scerosis (MS) patients with optic neuritis compared to healthy controls, even in MS patients with no history of optic neuritis, RNFL may still be decreased in thickness consistent with a neurodegenerative disease model of MS.

►Inherited Retinal Degenerations
►Multiple Sclerosis
►Optic Neuritis
►Retinal Ganglion Cells

Optical Flow

►Optic Flow

Optical Illusions

►Visual Illusions

Optimal Control

Definition
Optimal Control is a particular control technique in which the controller is designed to minimize a certain

performance index. For example, in human postural control, the performance index may be a combination of center of mass variance and mean squared ankle torque.

►Adaptive Control
►Modeling of Human Postural Control
►Motor Control Models

Optimal Control Theory

Definition
The mathematical theory of how controllers should be designed to achieve optimal performance.

►Neural Networks for Control

Optimal Muscle Length

Definition
The optimal length of a muscle is defined as the length at which a muscle can exert its maximal isometric steady-state force.

►Force Depression/Enhancement in Skeletal Muscles
►Length-tension

Optimization

Definition
An algorithm to achieve a particular goal while minimizing one, or a set of criteria. Mathematical optimization is defined by minimizing, maximizing, or optimizing a specific function (typically called the objective or cost function) while simultaneously satisfying any equality and/or inequality constraints. Mathematical Optimization has been the preferred approach to solve the distribution problem in biomechanics.

►Distribution Problem in Biomechanics
►Motor Control Models

Optimization Model for Motor Control and Learning

Definition
Computational models based on the idea that motor control and learning are planned and executed so as to achieve a behavioral goal, namely a tradeoff between task performance, body stability, and energy consumption. These models explain invariant movement features as a result of optimality and motor learning as a relaxation process toward a global minimum of a behavioral goal. Voluntary arm reaching, for example, has been modeled as smoothness or accuracy maximization, and locomotion as gait optimization in such a way as to maximize traveling distance using minimal muscle work.

►Theories on Motor Learning

Optocollic Reflex

Definition
A reflexive compensatory head movement elicited in response to motion of the entire visual world.

►Visual-Vestibular Interaction

Optogenetic

Definition
A method to manipulate the activity of genetically identified neurons using light-sensitive ion channels.

►Hypocretin/Orexin

Optokinetic After-Nystagmus (OKAN)

Definition
When subjects are placed in darkness following optokinetic nystagmus, the nystagmus continues and

the slow phase velocity has characteristics similar to Per- and Post-Rotatory Nystagmus. The presence of OKAN can be directly related to activation of velocity storage.

►Optokinetic Nystagmus
►Per-rotatory Vestbular Nystagmus
►Velocity Storage

Optokinetic Nystagmus (OKN)

Definition

A physiological nystagmus that occurs when a large part of the image moves uniformly over the retina, such as when viewing objects from a moving train or turning around. It consists of two components of eye movements: slow phase, which moves the eyes to follow the visual scene motion (called optokinetic response), and quick phase, which rapidly reset the eye position deviation by slow phase.

►Nystagmus
►Optokinetic Response

Optokinetic Reflex

Definition

►Optokinetic Nystagmus (OKN)

Optokinetic Response

Definition

Compensatory head, eye and body movements in response to motion of the entire visual world. They function to control gaze, posture and locomotion (alternatively known as optomotor responses).

►Visual-Vestibular Interaction

Optokinetic Response Adaptation

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Definition

Optokinetic response (OKR) adaptation is a behavioral change and underlying neural process that increases the ability of the optokinetic system to move the eyes and track moving large-field visual stimuli (see ►Optokinetic nystagmus). The adaptation is stimulated by motion of the visual image across the retina (►Retinal slip), and is prominent in species where the performance of the optokinetic system is normally low, such as rodents and fish. The increased efficacy of the OKR acts to reduce image motion across the retina and thereby improve visual acuity.

Methods to Produce and Measure Adaptation

Methods to produce and measure OKR adaptation are an extension of those used to produce and measure OKR itself. Subjects typically sit at the center of a large cylindrical drum with a visual pattern on the inside that takes up most of the subject's visual field (Fig. 1).

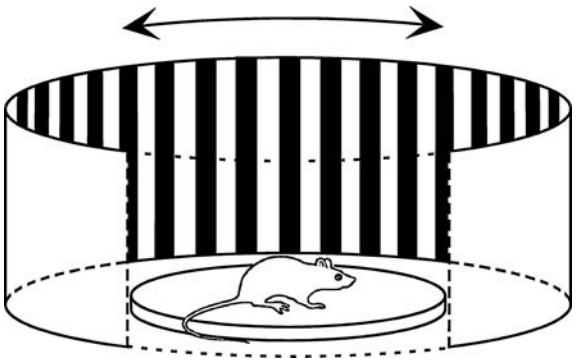
Oscillation of the "optokinetic drum," usually in a horizontal plane, evokes eye-movements that tend to track the motion of the drum (see Optokinetic eye movements). The ability of the eye-movements to track drum motion is often measured as gain, which is the ratio of eye angular velocity to drum angular velocity. Perfect tracking would produce equal eye and drum velocities and a gain of 1.0. Actual gains are always less than one, and cannot exceed one.

Whereas measurement of OKR gain requires only a few minutes, continued drum motion is used to produce adaptation. Adaptation takes place anytime there is retinal slip, but a measurable change in OKR gain requires an hour or so of drum oscillation. Figure 2 illustrates adaptation in a rabbit. OKR gain at the start of adaptation is about 0.5 (eye movement only compensates half of the drum motion). After an hour, OKR efficacy has increased to 0.74, and an additional two hours of adaptation increases gain only slightly more to 0.78.

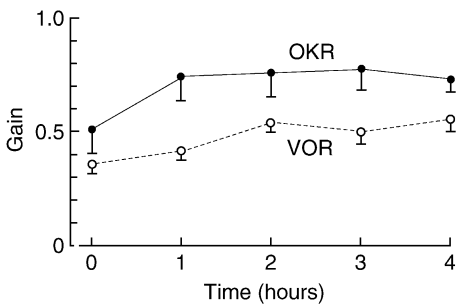
Characteristics

Species Dependencies

OKR adaptation has mainly been observed in rodents [1–3] and goldfish [4] where the gain of the OKR is typically well below 1.0 except at very low drum velocities. This is in part because gains less than one allow adequate retinal slip to produce adaptation in a suitable paradigm, and there is sufficient room below the maximum gain of one for the increased OKR efficacy to



Optokinetic Response Adaptation. Figure 1
Illustration of the apparatus used to generate and adapt the optokinetic response. A mouse sits on a stationary platform surrounded by an optokinetic drum which oscillates back and forth about a vertical axis. The mouse would be restrained in an actual experiment. The drum is illustrated as being lined on the inside with vertical black and white stripes, but other high contrast patterns have been used. Vestibular responses can be produced by rotating the platform on which the mouse sits. To induce the vestibuloocular reflex (VOR), rotation takes place in the dark, but various VOR adaptation paradigms combine rotation of the mouse with motion of the optokinetic drum in the light.



Optokinetic Response Adaptation. Figure 2 Plot of the gain of the optokinetic response (OKR – solid line) as a function of the duration of OKR adaptation. OKR gain increases rapidly in the first hour and then plateaus. The paradigm for increasing OKR gain also has the effect of increasing the gain of the vestibuloocular reflex (VOR – dotted line) in rodents. Figure adapted from Nagao et al. [6].

be observed. In one case where OKR gain was close to one at low drum velocities, the effect of OKR adaptation could still be observed at higher drum velocities where OKR gain normally drops well below one [2].

OKR adaptation has not been reported in primates, but neither has it been systematically tested. The excellent tracking of optokinetic targets at velocities less than 60°/s leaves little opportunity for adaptation to occur or to be observed. Moreover, differences between primate and rodent physiology argue that OKR adaptation is less likely in primates. Primates lack the directionally selective retinal ganglion cells that participate in rodent OKR, they have a fovea instead of a visual streak, and ►smooth pursuit rather than OKR dominates primate responses to motion in the visual field.

Velocity Dependence

OKR adaptation has been produced using optokinetic drum velocities past the limit at which the eyes reliably track the drum. In rodents, this is at low stimulus frequencies (0.1–0.4 Hz) and at peak drum velocities of 3°/s–10°/s. Retinal slip velocities are then between 2°/s and 8°/s. It has been reported that low retinal-slip velocities (<1°/s) do not produce adaptation [3], but this has not been extensively tested.

OKR Adaptation and Head Movement

The vestibulo-ocular reflex (VOR), which is not a visual-following reflex, acts to counter-rotate the eyes in the head whenever the head moves with the goal of stabilizing the visual scene on the retina (see ►VOR). Adaptation of the VOR occurs when this ocular compensation is imperfect, or in other words, when movement of the head produces retinal slip (see ►VOR adaptation). This retinal slip might be expected to produce OKR adaptation as a byproduct, and indeed it does [1,2]. This is best demonstrated by using different combinations of forced head motion and drum motion in order to create retinal slip velocities that are either in the same or opposite direction as eye motion. For instance, when the drum motion is in the opposite direction as head motion (a paradigm that increases VOR gain), slip velocity is in the same direction as eye velocity. However, when drum motion is in the same direction as the head motion (a paradigm that decreases VOR gain), slip velocity is in the opposite direction as eye velocity. In rodents, both paradigms produce OKR adaptation and the effect of both is to increase OKR gain [1,2]. Apparently retinal slip of any kind augments OKR gain in these animals.

However in monkeys and cats, the situation is different [5]. Paradigms that increase VOR gain also increase OKR gain, and those that decrease VOR gain also decrease OKR gain. In each case, the result is to improve the VOR in the sense that there is less retinal slip during head rotation at the end of the particular paradigm, but the concomitant reduction of OKR gain is maladaptive. This has been interpreted to mean that the primary function of the adaptive mechanisms is to adjust VOR gain, but that the VOR and OKR pathways share a common structure that changes the gain of both systems simultaneously.

Finally, there is the possibility that the OKR-adaptation paradigm (drum motion with no head motion) could

alter the VOR because of the retinal slip. In rodents and goldfish, this paradigm does increase the gain of the VOR [1,4,6] (Fig. 2). However in monkeys, the effect is negligible [7]. The above differences between rodents and primates reinforce the idea that primates are not the same as rodents and goldfish regarding the existence of OKR adaptation.

Upstream Conditions

As noted above, the existence of retinal slip of adequate velocity is required for OKR adaptation to occur.

Involved Structures

Adaptation of the OKR presumably involves plasticity at synapses that are part of the normal OKR pathway (see ►Optokinetic eye movements). In most species, this involves indirect projections of from the accessory optic system to the floccular lobe of the cerebellum and then to the vestibular nuclei. Rodents may have an additional pathway that has not been found in primates from the pretectum directly to the vestibular nuclei.

Experimental interventions that diminish or abolish OKR adaptation precisely parallel those that diminish or abolish adaptation of the VOR (see VOR adaptation and ►Flocculus hypothesis). Among these interventions are those known to disrupt long-term depression (LTD) at the cerebellar parallel-fiber to Purkinje-cell synapse. They include destruction or inactivation of the flocculus [6], destruction of the climbing-fiber afferent pathway to the cerebellum [3], disruption of metabotropic glutamate receptors either by direct blockage or by elimination in mutant mice [8], blockage of nitric oxide synthase [9], and disruption of phosphokinase C. The first two appear to implicate the flocculus in OKR adaptation, but the latter four are not necessarily specific. Measurements of Purkinje-cell activity during adaptation show that changes do occur within the flocculus, and that the changes probably produce the changes in OKR gain rather than reflect feedback from the altered eye velocity [6]. In different experiments, physiological changes have also been observed in synapses the vestibular nuclei [10]. Shutoh et al. [10] argue that short-term plastic changes (about a day) reside in the flocculus while long term plastic changes reside in the vestibular nuclei. As has been strongly indicated for the VOR, it seems likely that plastic changes of some sort occur in both the flocculus and the vestibular nuclei.

References

1. Collewijn H, Grootendorst AF (1979) Adaptation of optokinetic and vestibulo-ocular reflexes to modified visual input in the rabbit. Prog Brain Res 50:771–781
2. Nagao S (1983) Effects of vestibulocerebellar lesions upon dynamic characteristics and adaptation of vestibulo-ocular and optokinetic responses in pigmented rabbits. Exp Brain Res 53:36–46
3. Katoh A, Kitazawa H, Itohara S, Nagao S (1998) Dynamic characteristics and adaptability of mouse vestibulo-ocular and optokinetic response eye movements and the role of the flocculo-olivary system revealed by chemical lesions. Proc Natl Acad Sci USA 95:7705–7710
4. Marsh E, Baker R (1997) Normal and adapted visuo-oculomotor reflexes in goldfish. J Neurophysiol 77:1099–1118
5. Lisberger SG, Miles FA, Optican LM, Eighmy BB (1981) The optokinetic response in monkey: underlying mechanisms and their sensitivity to long term adaptive changes in V.O.R. J Neurophysiol 45:869–890
6. Nagao S (1989) Role of cerebellar flocculus in adaptive interaction between optokinetic eye-movement response and vestibulo-ocular reflex in pigmented rabbits. Exp Brain Res 77:541–551
7. Lisberger SG, Miles FA, Zee DS (1984) Signals used to compute errors in monkey vestibuloocular reflex: possible role of flocculus. J Neurophysiol 52:1140–1153
8. Shutoh F, Katoh A, Kitazawa H, Aiba A, Itohara S, Nagao S (2002) Loss of adaptability of horizontal optokinetic response eye movements in mGluR1 knockout mice. Neurosci Res 42:141–145
9. Katoh A, Kitazawa H, Itohara S, Nagao S (2000) Inhibition of nitric oxide synthesis and gene knockout of neuronal nitric oxide synthase impaired adaptation of mouse optokinetic response eye movements. Learn Mem 7:220–226
10. Shutoh F, Ohki M, Kitazawa H, Itohara S, Nagao S (2006) Memory trace of motor learning shifts transsynaptically from cerebellar cortex to nuclei for consolidation. Neuroscience 139:767–777

Optomotor Response

Definition

In a broad sense the motor response to a visual stimulus. In narrower sense, the response of an animal to wide-field, visual stimulation (synonym: optokinetic response).

Oral Mucosa

Definition

The epithelium lining the inside of the mouth, the tongue and the palate.

►Tactile Sensation in Oral Region

Oral-facial Dyskinesias

Definition
Repetitive, rhythmic, bizarre movements in the face region.

Orbital Dynamics

►Oculomotor Dynamics

Orbital Pulleys

Definition
When the eyes move from the primary position, the eye muscles do not slide freely within the orbital tissue. Instead their paths are restricted, possibly by rings of connective tissue and smooth muscle that have been termed orbital pulleys.

►Eye Orbital Mechanics

Orbital Tissues Definition

Orbital tissues are the fat and connective tissues that surround the eyeball in the bony orbit.

►Eye Orbital Mechanics

Orbitofrontal Cortex

Definition
The orbitofrontal cortex is a region situated at the ventral surface of the frontal part of the brain. It is the subpart of the prefrontal cortex that receives projections from the magnocellular medial nucleus of the mediodorsal thalamus. The orbitofrontal cortex is an important brain region for the processing of rewards and punishments. The medial orbitofrontal cortex activity is related to monitoring the reward value of many different reinforcers, whereas lateral orbitofrontal cortex activity is related to the evaluation of punishers, which may lead to a change in ongoing behavior. The subjective hedonic experience is mediated by mid-anterior orbitofrontal cortex.

Orexigenic

Definition
Orexigenic means possessing activity that stimulates food intake. [Anorexigenic: opposite of orexigenic.]

►Neuropeptides

Orexin/Hypocretin

Definition
Orexins (OxA and OxB) are two neuroexcitatory peptides derived from the same precursor produced in a few thousand neurons restricted to the perifornical area of the hypothalamus. The orexins bind to two receptors (Ox1 and Ox2). Orexin is a synonym of hypocretin, and was given its name (orexi, appetite in Greek) because of initial studies showing increase in food intake following infusion of pharmacological doses of the peptides in the brain. The orexin/hypocretin system stabilizes wakefulness and sets the arousal threshold, enhances catabolism and is a gate to drug reinstatement. Dysfunctional orexin may be associated with the sleep disorder narcolepsy.

►Brain States and Olfaction
►Hypocretin/Orexin
►Memory and Sleep
►Narcolepsy
►Nocturnal/Diurnal
►Sleep – Motor Changes
►Sleep – Sensory Changes
►Ventrolateral Preoptic Nucleus (VLPO)

Organ Discharge

►Electric Organ Discharge

Organ of Corti

Definition

The mammalian organ of hearing proper, lying between the basilar membrane and the tectorial membrane of the cochlea. It contains the inner hair cells, the outer hair cells and the peripheral synapses of the afferent and efferent neurons of the auditory nerve.

►Cochlea

Organizational Hormonal Effects

Definition

Hormone-induced alterations occurring during the early development of an organism that give rise to chronic changes in structure and/or function of particular anatomic systems. For example, manipulating the gonadal hormonal milieu of neonate rodents can produce durable effects on the developing nervous system resulting in lifelong changes in nociception and antinociception.

►Gender/sex Differences in Pain

Organizer

Definition

Area, tissue or cell group of an embryo able to produce signals (or signaling proteins) that have an effect at a distance on the fate of adjacent tissue, in a concentration dependent manner (this requires the expression of specific receptors in the tissue). Examples of organizers are the node and the notochord, which produce signals that have an effect either on the ectoderm (node signals related to neural induction) or on the ventral neural plate/tube (notochord signals related to dorsoventral patterning). These are cases of organizers acting early in development and are many times referred to as "primary organizers." Later in development, there are "local organizers" inside the neural tube having an effect on patterning and specification of adjacent areas (for example, the isthmic organizer or the zona limitans intrathalamica). These local organizers of the neural tube that appear later in development are called "secondary organizers."

►Evolution and Embryological Development of the Forebrain
►Node
►Notochord

Organizing Centers and Patterning

Definition

Restricted regions of the embryo that secrete specific signalling molecules, responsible for specifying distinct domains (molecularly, anatomically, functionally distinct) in competent neighbouring tissues. This process is called patterning.

►Evolution of the Brain: In Fishes
►Evolution of the Telencephalon: In Anamniotes

Orientation Behavior

Definition

Ability to move in space either with respect to an external reference system (passive) or by actively generating spatial information (like in echo location).

Orientation Selectivity in Vision

Definition

Neurons in the retina and lateral geniculate nucleus of the thalamus are sensitive to local changes in light

levels, much like sensors in a digital camera. But these cells are not able to resolve higher order features of the visual scene. By contrast, cortical cells respond best to elongated contours, or edges, formed by extended boundaries between relatively dark and bright regions of the image – contrast borders. Importantly, almost all cortical neurons are orientation selective: individual cells are strongly excited by contours that share a common spatial orientation but respond weakly if at all to stimuli tilted perpendicular to the optimal angle. Different neurons prefer different stimulus orientations. Also, some neurons are tuned to a narrow range of stimulus angles while others are less selective. Orientation selectivity is the most widely studied aspect of visual cortical function; its origin in different species and its role in visual processing remain a subject of great interest.

►Visual Cortical and Subcortical Receptive Fields

Orientation Sensitivity in Cutaneous Mechanosensation

Definition

Subjects can discriminate a 10% angular difference in the orientation of a cylinder indented into the fingertip. Discriminating the orientation of a grating (usually vertical vs. horizontal) is also used to assess spatial resolution. Orthogonal gratings can be discriminated for groove widths around 1 mm at the fingertips and around 4 mm at the more proximal regions of the fingerpad.

►Processing of Tactile Stimuli

Orienting Linear Vestibulo-ocular Reflex (IVOR)

Definition

The reflex that responds to low frequency linear accelerations of the head in space to produce eye movements that tend to align the coordinate frame of the eyes with the net direction of the linear or equivalent linear acceleration of the head. This has also been referred to as the tilt response.

►Vestibuloocular Reflexes

Orienting Movement

Definition

►Orienting Reflex

Orienting Reflex

Definition

Also known as orienting response(s). In a general sense, it is the complex behavioral pattern aimed at optimizing the perception of biologically significant events in the environment and to make rapid and efficient choice of an appropriate motor response. Orienting is truly "reflexive" toward particularly intense or previously unexperienced, novel sensory stimuli. Accordingly, the Pavlovian school used the term "what happens?-reflex." Its earliest manifestation is the generalized alerting. Sensory events signaling a potential danger or a positive reinforcement, such as prey for a predator or food delivery for an operantly conditioned animal, are also highly efficient to induce orienting. Motor responses to such stimuli are, respectively, either avoidance or approach. To make the choice between these strategies, the source of the stimulus must be rapidly identified. Alignment of the line of sight on the stimulus (gaze shifting) is the most important motor component of orienting reflex in animals whose behavior is dominated by vision and, in particular, in those having a small central region of the retina specialized for fine-grain visual discrimination (e.g., fovea in primates, area centralis in felines).

►Operant Conditioning
►SC-Tectoreticulospinal neurons (TRSNs)
►Vision

Orienting Responses

Definition

Movements that direct the line of sight and/or the ears towards sensory stimuli.

Orthodromic Action Potential Propagation

Definition

Propagation of action potentials in the naturally occurring direction (from "orthos", Greek for straight, correct; "dromos", Greek for run).

►Action Potential Propagation

Orthostatic Intolerance

Definition

Orthostatic intolerance is difficulty in maintaining standing posture due to orthostatic hypotension. Astronauts returning on Earth after spaceflights often complain of this symptom. Similar orthostatic problems occur after long-term bed rest.

►Autonomic Function in Space

Oscillations and Plasticity in the Olfactory System

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Definition

Learning induces neural assemblies formation detectable in the network through modulation of oscillatory activities.

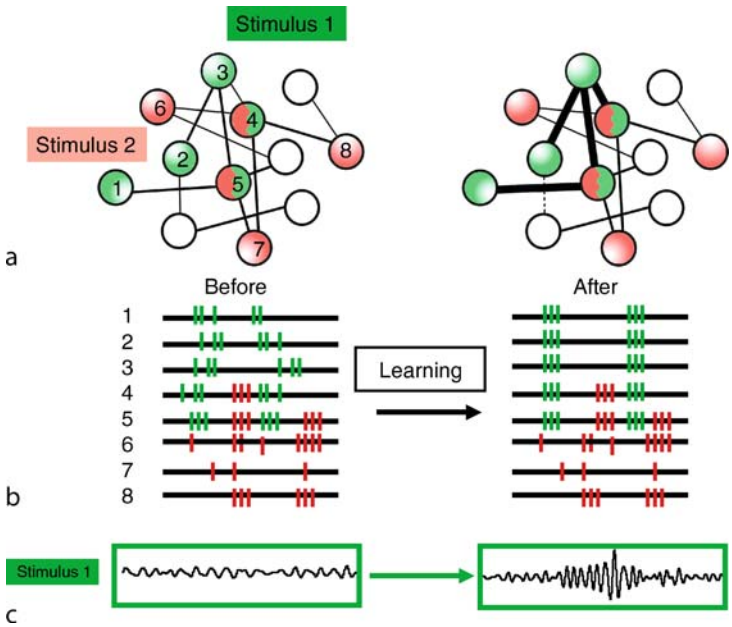
Characteristics

The Concept of Neural Assemblies

Current theories put forward that information storage in the brain relies on changes in functional interactions within widely distributed neural areas. This concept of distributed memory suggests in turn the idea that stimuli representations could be achieved through assemblies of simultaneously active neurons. Such assemblies could be found within a given structure or between distinct neural areas. As a consequence, memory should be considered as a dynamical process involving spatio-temporal patterns of reactivation of previously reinforced neural ensembles within and across different brain areas. These assemblies involve both sensory and limbic areas.

If we accept this concept of distributed representations one have to face the problem, commonly addressed as the "binding problem" of how such distributed activities could be put back together to elicit stable and unambiguous representations of objects in the brain. Indeed, according to this theory a given neuron would be able at different time to take part to different stimuli representations. As a consequence, neuronal elements belonging to the same assembly must be identifiable and differentiated from members of other assemblies (see Fig. 1). Twenty years ago, von der Malsburg proposed that neurons joining into an assembly should establish temporal synchronization on a millisecond time scale. This temporal tagging has two major advantages: Synchronization of neuronal activities facilitates signal transmission to target structures because temporal coincidence of action potential volleys on post-synaptic higher areas increases probability of eliciting action potentials. In addition, this coincidence is very important in voltage-dependent processes like NMDA-receptor-gated conductance which are of prime importance in induction of synaptic plasticity.

Synchronous activities in assemblies often occur in a repetitive way and give rise to well-known brain rhythms also called oscillations. They can be recorded with macro electrodes either directly from the scalp (electroencephalogram, EEG) or from intracerebral inserted electrodes (►local field potentials, LFPs). They have been observed in many different brain areas especially those showing a laminar organization like cortices. These oscillations of LFPs exhibit a large variety of frequencies from 1 to 100 Hz depending on the vigilance state (arousal, attentiveness, sleep, etc.) or the presence of a sensory stimulation or the necessity to control a motor behavior. The origin of oscillations is still a matter of debate but one major hypothesis is that they could be an emergent property of a given network resulting from inhibitory interneurons and reciprocal connections. In relay neurons of any cortical area, these oscillations likely reflect current source generated by neuronal synaptic input in the dendritic tree and action potentials generated at the cell body level. LFP activities are a good indicator of how and when a large set of neurons synchronize and desynchronize during information processing. This review will illustrate how the study of the mammalian olfactory system brings information on the functional significance of neural oscillations in sensory processing and memory.



Oscillations and Plasticity in the Olfactory System. Figure 1 Illustration of the concept of neural assemblies. (a). As symbolized by the colour code, each stimulus co activates a specific ensemble of neurons. However, some neural elements (4 and 5) could be co activated by both stimuli. Learning of stimulus 1 is associated with reinforcement of synaptic contacts between neurons previously co activated by this stimulus (*thick lines*). (b). Temporal organization of the discharge of each neuron clearly differentiates two neural assemblies (in green for stimulus 1 and red for stimulus 2). Neurons 4 and 5 could take part to both representations depending on their discharge timing. Before learning, units taking part to the same assembly are simply co-activated. Repeated presentation of stimulus 1 refines of neural discharge synchronization. As a consequence, the amplitude of ►local field potential oscillatory activity is increased and the dominant frequency corresponds to the periodicity of the synchronization.

Oscillatory Activities in the Olfactory System

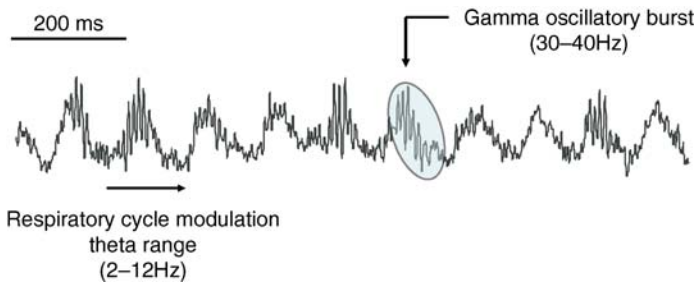
In the mammalian olfactory system, Adrian in the 50's initially described prominent oscillations in field potential activities. In ►awake animals, in the absence of any olfactory stimulation, the signal derived from the first relay of olfactory processing, the olfactory bulb, exhibits a well structured activity as shown on Fig. 2.

Slow modulations of LFP associated with inhalation are easy to observe. These high amplitude oscillations are in the theta range (2–12 Hz). They have been shown to follow the respiratory activity and hence might vary in frequency. Moreover, during period of exploration associated with active sniffing, the respiratory modulation has a frequency range which overlaps with the theta activity typically observed in limbic areas such as the hippocampus (4–12 Hz).

Recordings also show regular spindle bursts of oscillations during each inspiration phase of the respiratory cycle. This second type of oscillatory activity is in the gamma range (30–90 Hz). Interestingly, in a given animal, even in the absence of any olfactory stimulus, the distribution of amplitude of gamma bursts forms a stable map at the surface of the OB. Presentation of an odor in a specific experimental context modifies this distribution. However, this new map is more related to the behavioral meaning of the stimulus than to its chemical quality. Indeed, if the same odor is presented in another context, a different map is obtained [1]. Recently, Kay [2] proposed to distinguish two types of gamma activity, type 1 (65–90 Hz) corresponding to the bursts associated to the peak of inhalation and type 2 (35–65 Hz), lower in frequency. These rhythms seem to be associated with different behavioral features and are likely to be produced by different synaptic interactions within the olfactory bulb.

Whereas gamma and theta activities have been studied for a long time, at first, little attention was paid to an intermediate type of periodic activity in the beta range (15–35 Hz).

This activity has now been reported by several authors to be selectively associated with ►odor sampling not only in the olfactory bulb, but also at higher level of olfactory processing like the piriform cortex and lateral entorhinal cortex. These studies pointed out to a more or less prominent increase in the amplitude of this oscillatory activity in response to behaviorally relevant odors [3,4] or odors experimentally associated with a reward [5–8].



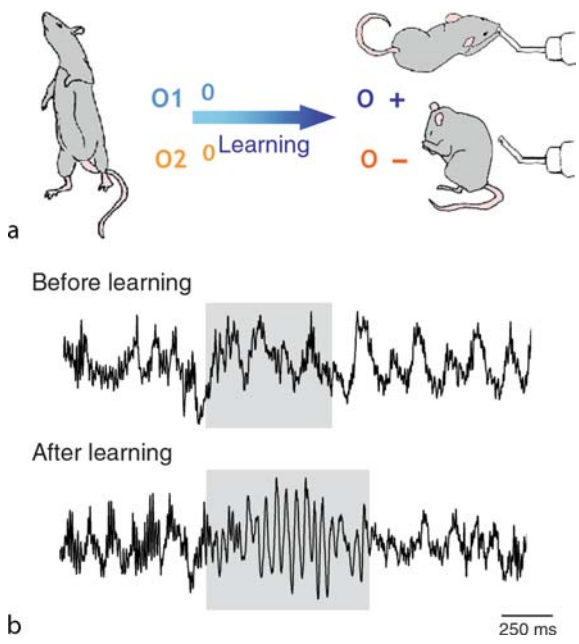
Oscillations and Plasticity in the Olfactory System. Figure 2 Spontaneous activity recorded in the olfactory bulb in ►awake animal.

Thus, both gamma and beta oscillatory activities were associated to perception and cognitive processing of olfactory stimulus. In awake animals, gamma oscillatory activity is prominent in the absence of odor and seems more related to attention toward an expected stimulus or a given experimental context. Beta oscillatory activity has never been reported in the absence of odor. This activity emerges during odor sampling and is modulated both by the chemical nature of the odor and its behavioral significance.

Oscillations and Construction of Odor Representations

According to the concept of neural assemblies proposed above, synchrony in a given neural network favors both signal transmission and synaptic plasticity. Hence, if this view is correct one could predict that olfactory learning should induce reinforcement of excitatory transmission between cells responding to the odor to be learned. As a consequence, learning should modify oscillatory regimes associated with the processing of learned odors. A first step toward the experimental demonstration of this hypothesis has been made by a few studies in which multisite neural recordings were performed in animals engaged in two different olfactory discrimination learning paradigms [7–9].

In the first paradigm (see Fig. 3), two odors without any a priori ►behavioral signification (►odor with behavioral signification) were assigned with two different values by pairing their presentation either with a sweet (O+) or a bitter (O−) solution. At the beginning of the experiment, the two odors induced the same behavioral response but after a few experimental sessions, thirsty rats exhibited a differential response to each odorant. Indeed, they learnt to run promptly to drink when O+ was delivered and avoid drinking when O− was presented. In parallel to this behavioral response modification, a clear oscillatory activity in the beta band (near 27 Hz) emerged in the olfactory bulb in response to odors used in the learning paradigm. In respect to a potential role in olfactory coding, we found that this activity exhibited different characteristics in amplitude and latency according to the recorded region



Oscillations and Plasticity in the Olfactory System. Figure 3 Learning-induced modulation of beta oscillatory activity. (a). Experimental protocol. Two odors without any a priori behavioral signification (O1 and O2) are assigned with two different values by pairing their presentation either with a sweet (O+) or a bitter (O−) solution. (b) Comparison of odor-induced activity in the olfactory bulb before and after O1 has acquired a positive value for the rat. The shaded zone corresponds to the odor sampling period. After learning, an oscillatory burst in the beta range (around 27 Hz) is clearly observed.

in the olfactory bulb (anterodorsal vs. posteroventral) and the chemical nature of the odorants. More interestingly, the large beta oscillatory activity emerged a few trials before the animal reached the criterion level. As a whole, results stressed out the possible role of the beta oscillatory activity in both odor representation and olfactory recognition. The same type of activity

was also found in other structures involved in odor stimulus processing like the piriform cortex. Moreover, a pharmacological inactivation of feedback connections from piriform cortex to olfactory bulb prevented in both structures the emergence of beta activity in response to learned odors suggesting that this oscillatory activity could be the signature of a neural network set up through learning and involving well-known reciprocal excitatory cortico-cortical connections between the olfactory bulb and the piriform cortex.

Recently, using a two-alternative choice odor discrimination, Beshel and colleagues [9] also showed a functional link between gamma range oscillatory activities in the OB and plasticity. In this paradigm, task demand was manipulated using either dissimilar or similar odorants ("coarse" vs. "fine" discrimination). Gamma oscillatory power progressively increased over the course of fine discrimination learning in contrast to coarse discrimination. This modulation was specific to gamma frequency range (65–85 Hz) and independent of changes in the theta or beta frequency range. It was also restricted to the OB despite gamma activity was also reported during spontaneous activity in the piriform cortex. This experimental result is in favor of a functional role of gamma oscillatory activity in pattern disambiguation. However, in mammals, data establishing a direct link between oscillatory activity disruption and behavioral performance alteration are still lacking.

Until now, the only demonstration that oscillatory synchronization might play a determinant role in fine stimulus encoding and odor recognition was brought by a work on honeybees [10]. In this animal model, odors evoke oscillatory synchronizations of groups of neurons in the antennal lobe, a structure functionally equivalent to the vertebrate olfactory bulb. These oscillations, in the beta range (around 30 Hz) could be selectively disrupted with picrotoxin, a pharmacological antagonist of $GABA_A$ receptors without affecting neural response and selectivity to odors. Behavioral experiments combining pharmacological disruption of odor-evoked oscillatory activity and evaluation of olfactory discrimination performance showed that picrotoxin-treated animals failed to discriminate between similar odorants although they were unimpaired for coarse discrimination. These observations were the first real argument for a role of neural synchronization in separation of spatially overlapping neural networks. It is of course tempting to speculate that neural oscillatory synchronization might play a similar role in other animal models.

In conclusion, one can point out that the detailed investigation of neural rhythms through LFPs recordings in behaving animals brings important insight on neural correlates of sensory discrimination and recognition. One of the main advantages of this approach is the relative ease with which one can obtain signal from several recording sites simultaneously and over the course of training (several days). This allows investigation of some neural correlates which sustain learning and memory in a time scale which characterized many forms of knowledge acquisition.

References

1. Freeman WJ, Schneider W (1982) Changes in spatial patterns of rabbit olfactory EEG with conditioning to odors. Psychophysiology 19:44–56
2. Kay LM (2003) Two species of gamma oscillations in the olfactory bulb: Dependence on behavioural state and synaptic interactions. J Integr Neurosci 2(1):31–44
3. Zibrowski EM, Vanderwolf CH (1997) Oscillatory fast wave activity in the rat pyriform cortex: relations to olfaction and behaviour. Brain Res 766:39–49
4. Chabaud P, Ravel N, Wilson DA, Mouly AM, Vigouroux M, Farget V, Gervais R (2000) Exposure to behaviourally relevant reveals differential characteristics in rat central olfactory pathways as studied through oscillatory activities. Chem. Senses 25:561–573
5. Boeijinga PH, Lopes da Silva F (1989) Modulations of EEG activity in the entorhinal cortex and forebrain olfactory areas during odour sampling. Brain Res. 478:257–268
6. Ravel N, Chabaud P, Martin C, Gaveau V, Hugues E, Tallon-Baudry C, Bertrand, Rémi Gervais (2003) Olfactory learning modifies the expression of odour-induced oscillatory responses in the gamma (60–90 Hz) and beta (15–40 Hz) bands in the rat olfactory bulb. Eur J Neurosci 17:350–358
7. Martin C, Gervais R, Hugues E, Messaoudi B, Ravel N (2004) Learning modulation of odor-induced oscillatory responses in the rat olfactory bulb: a correlate of odor recognition? J Neurosci 24(2):389–397
8. Martin C, Gervais R, Messaoudi B, Ravel N (2006) Learning-induced oscillatory activities correlated to odour recognition: a network activity. Eur J Neurosci 23:1801–1810
9. Beshel J, Kopell N, Kay LM (2007) Olfactory bulb gamma oscillations are enhanced with task demands. J Neurosci 27(31):8358–8365
10. Stopfer M, Bhagavan S, Smith BH, Laurent G (1997) Impaired odour discrimination on desynchronization of odour-encoding neural assemblies. Nature 390:70–74

Oscillations in the Brain

Definition

Oscillation is the variation, typically in time, between two boundary values of some measure. In the brain, oscillatory activities have been widely observed. At the level of the neurons and networks of neurons, it has been shown that intrinsic (mainly due to ion channel) and networks properties (connectivity, inhibition and excitation), endowed the neuron and the network with

dynamical properties, including abilities to oscillate at multiple frequencies. Oscillations are groups into category that depend on their frequency and their relation with particular behaviors. Among other one can distinguished oscillations in the gamma band (30–90 Hz) that have been involved in perception, problem solving, fear and other higher brain function.

►Brain Rhythms
►Network Oscillations
►Network Oscillations in Olfactory Bulb

Oscillator

Definition

A device that generates a periodic signal.

►Signals and Systems

Oscillator for Circadian Rhythm

Definition

A system that produces rhythmic output or whose state varies in a periodic fashion in the absence of external stimuli. A circadian oscillator produces a rhythm whose period is approximately 24 h when the organism is maintained in constant conditions. This may be detected in the cycle of activity and rest, in gene expression as reflected by mRNA abundance or protein concentration, etc. Negative feedback loops involving regulation of transcription by translational products have been found to generate such circadian oscillations in a number of organisms. Circadian oscillators are typically entrainable by environmental cues within a range of periods close to 24 h, and often vary little in period over a range of temperatures.

Oscillator Versus Hourglass Timers

Definition

Time-measurement can be achieved by different types of mechanisms that change state in a predictable way before returning to the starting point. Once started, an oscillator may continue to generate cycles (have an endogenous rhythm) indefinitely, or it may damp out. In contrast, an hourglass measures a fixed interval and then must be restarted (by some external stimulus) in order to measure a second interval. Whether a biological system acts as an oscillator or as an hourglass can be a function of its environment; changes in parameters may alter the behavior of an oscillator so that it damps rapidly and thus functions as an hourglass.

Osmolality

Definition

Osmolality refers to the total concentration of all particles that are free in a solution. Thus, glucose contributes one particle, whereas fully dissociated NaCl contributes two. In all body fluid compartments, humans have an osmolality – expressed as the number of osmotically active particles per kilogram of water – of approximately 290 mOsmoles/kg water (290 mOsm).

Osmotic Energy

Definition

The energy associated with a concentration gradient.

►Energy/Energetics

Osseoperception

Definition

The tactile sense relayed through dental impacts placed in the jaws to serve as replacements for lost teeth.

►Tactile Sensation in Oral Region

Osteoarthritis

Definition

Osteoarthritis is a joint degenerative disease characterized by the breakdown of articular cartilage, osteophyte formation, joint swelling, stiffness and pain. The

disease progresses from an initial hypertrophy of the articular cartilage to degeneration of the cartilage and underlying bone. Osteophytes also grow throughout the affected joint.

►Articular Cartilage
►Measurement Techniques (Pressure)

Osteoblast

Definition
Cell of fibroblast lineage responsible for secreting unmineralized bone matrix.

►Bone

Osteoclast

Definition
Cell of macrophage lineage responsible for resorbing bone.

►Bone

Osteocyte

Definition
Former osteoblasts, which are entombed within mineralizing matrix, reside within the bone in caverns termed lacunae, and appear to play an integral role in maintaining bone vitality and the tissue's ability to respond to altered loading states.

►Bone

Osteoporosis

Definition
A systemic disease in which bone mass and morphology have degraded sufficiently to elevate the risk of fracture.

►Bone

Osteostracans

Definition
A group of early jawless craniates that lived around 425–415 Ma BP and resembled gnathostomes in having pectoral fins, but not pelvic ones.

►The Phylogeny and Evolution of Amniotes

Other Minds Problem

Definition
The other minds problem is the problem of how we know (or are justified in believing) that other human beings exemplify mental properties similar to the ones we exemplify, given that their conscious mental life is not accessible from our third person point of view. The existence of other minds is typically justified by an argument from analogy, stated in its classic form by John Stuart Mill and Bertrand Russell, according to which one's own body and outward behavior are observably similar to the body and the behavior of others, so that one is justified by analogy in believing that they also exemplify similar mental properties.

►Epiphenomenalism

Otic Placode

Definition
Thickening of the ectoderm and precursor of the otocyst.

►Evolution of the Vestibular System

Otoconia

Definition
Dense calcium carbonate particles ("ear stones") that are attached to the gelatinous otolith membrane over the

utricular and saccular maculae. Otoconia serve as inertial sensors of linear acceleration.

►Evolution of the Vestibular System
►Peripheral Vestibular Apparatus
►Sacculus
►Utriculus

Otocyst

Definition
Invagination of the otic placode forming a cycst at first that later subdivides and gives rise to the complex adult three-dimensional structure of the labyrinth.

►Evolution of the Vestibular System
►Otic Placode

Otoencephalitis

Definition
Inflammation of the brain due to an extension from an inflamed middle ear.

Otolith

Definition
The vestibular receptor organ that responds to linear accelerations of the head. Otoliths contain receptor cells in a small patch of neuroepithelium termed the macula. Above the macula is a gelatinous membrane into which the stereocilia of the hair cells project. Otoconia lie embedded in and attached to the top of the membrane.

►Otoconia
►Peripheral Vestibular Apparatus

Otolith Organs

Definition
The parts of the vestibular labyrinth composed of the utricles and saccules that sense linear acceleration or equivalent linear acceleration of the head.

►Peripheral Vestibular Apparatus
►Sacculus
►Utriculus

Otx

Definition
Member of a gene family (orthodenticle)

►Evolution of the Vestibular System

Otx1, Hominids

►Evolution of the Vestibular System

Outer Hair Cells

Definition
The hair cells of the mammalian cochlea responsible for amplifying the vibrations of the basilar membrane and the hair cell stereocilia.

►Cochlea

Outer Plexiform Layer

Definition
Synaptic layer in the outer (distal) retina where photoreceptors make synapses with horizontal and bipolar cells.

►Inherited Retinal Degenerations

Output Unit

Definition
A model network neuron that provides the network response to activity propagated through hidden units due to signals received by input units.

►Neural Networks

Ovariectomize

Definition
Surgical removal of the ovaries.

Overdetermined System

Definition
A mathematical system is called overdetermined if it has more system equations than unknowns. Overdetermined systems typically do not have a solution.

►Distribution Problem in Biomechanics

Overfitting

Definition
Overfitting refers to a problem that can arise during the training of artificial neural networks (or other statistical learning systems). During training the network learns a mapping from the input domain to the desired output. The target of this process is to capture the underlying regularities in the data that are to be modelled. However, since there are, in general, limited amounts of training data, the network may learn to approximate these correctly, while failing to process new data appropriately. This is referred to as overfitting: the network has learned a function that is too complex, modelling not only the regularities of the dataset, but also its noise.

►Connectionism

Overhang (DNA)

Definition
When a restriction cleaves DNA asymmetrically a stretch of single stranded nucleotides is left. If the single stranded bases end in a 3' hydroxyl a 3' overhang remains. Similarly, a 5' overhang remains when the single stranded bases end in a 5' phosphate. Overhangs are often generated in molecular biology by use of DNA endonucleases. Larger overhangs of several nucleotides, such as those created by restriction endonucleases, are often called "sticky-ends" since a DNA molecule with complimentary sequence in the overhang region can anneal to each other. This phenomenon is used in molecular biology to piece together DNA molecules from different sources which are then covalently linked with DNA ligase.

►Serial Analysis of Gene Expression

Overlap Zone in Skeletal Muscle

Definition
The overlap zone in skeletal muscle designates the area of overlap between the contractile proteins actin and myosin. At short muscle length, the overlap zone is big, and for increasing muscle length, the overlap zone becomes smaller. When there is no overlap between actin and myosin (i.e. the overlap zone has vanished), active force production is not possible anymore.

►Actin
►Force Depression/Enhancement in Skeletal Muscles
►Myosin
►Sarcomere Structural Proteins

Overshadowing

Definition
The ability of a conditioned stimulus (CS) to elicit a conditioned response (CR) is reduced when its pairings

with the unconditioned stimulus (US) take place in the presence of another neutral stimulus. Assessment of the magnitude of overshadowing is made through comparison with a control group that receives only pairings of the CS and the US. This is one of several examples of cue competition or stimulus selection effects that prompted development of predictive-driven learning models.

►Theory on Classical Conditioning

Overshoot (of Action Potential)

Definition

Reversal of membrane potential during the action potential peak.

►Action Potential

Overtraining Syndrome (OTS)

Definition

When prolonged, excessive training stress are applied concurrent with inadequate recovery, many of the positive physiological changes associated with physical training are reversed with overtraining. Chronic physiological maladaptations and performance decrements occur. Throughout the twentieth century, many names have been given to this chronic maladaptive state (e.g., underperformance syndrome, sports fatigue syndrome), but presently the term overtraining syndrome (OTS) is used. A large number of symptoms associated with overtraining have been reported in the literature and categorized according to physiological performance, psychological/information processing, immunological, and biochemical parameters. It is also probable that other signs/symptoms typically associated with overtraining are evident before a deterioration in performance. These might include generalized fatigue, depression, muscle and joint pain, and loss of appetite. However, it is the decline in performance frequently associated with an increased volume or load of training that captures the attention of the athlete and coach.

►Stress Effects During Intense Training on Cellular Immunity

Owl

Definition

Mostly night active bird species of the order Strigiformes. The barn owl, especially, is a model system for investigating mechanisms of sound localization (see essay on “Sound localization in the barn owl”), depth vision and plasticity of the nervous system.

Oxidative Potential

Definition

Motoneurons, like the muscle fibers that they supply, derive their energy from metabolism that either requires oxygen or does not. The metabolism that does require oxygen to generate adenosine triphosphate for energy is referred to as oxidative energy, the cells having oxidative potential.

►Axonal Sprouting in Health and Disease
►Motoneuron

Oxidative Stress

Definition

Oxidative stress is a medical term for damage to animal or plant cells caused by reactive oxygen (ROS) and nitrogen (RNS) species, which include superoxide radical, singlet oxygen, peroxynitrite or hydrogen peroxide. It is defined as an imbalance

between prooxidants and antioxidants, with the former prevailing.

►Alzheimer's Disease – Oxidative Injury and Cytokines

Oxytocin

Neuropeptide secreted as hormone by the neurohypophysis and involved in labor, lactation and reproduction.

►The Hypothalamo Neurohypophysial System
►Hypothalamo-Pituitary-Adrenal Axis
►Stress and Depression

Oxytocinergic Central Pathways

Definition

Oxytocinergic central pathways are involved in reproduction, cognition, tolerance, adaptation and the regulation of cardiovascular and respiratory functions. Centrally released oxytocin would also give rise to sedation.

►The Hypothalamo Neurohypophysial System